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BY

WILLIAM HALE-WHITE, K.B.E.
M.D. (Lond.), M.D. (Dub.), LL.D. (Edin.)
CONSULTING PHYSICIAN TO GUY'S HOSPITAL

TWENTY-EIGHTH EDITION

REVISED BY
A. H. DOUTHWAITE
M.D., F.R.C.P. (Lond.)
PHYSICIAN TO GUY'S HOSPITAL

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Materia medica:

Printed in Great Britain

PREFACE TO TWENTY-EIGHTH EDITION

The demand for a further edition of this work fortunately coincided with the appearance of the British Pharmacopœia of 1948. Although this official publication has been kept up-to-date by addenda since the last issue in 1932, the latest work embraces a vast number of new drugs and preparations. As well as 155 additions, the **B.P.** shews nearly 200 deletions, 27 changes of nomenclature, and also many alterations of dosage. All the important changes in these respects have been included in this book. The reader will note with satisfaction the disappearance from official status of many useless preparations, and the return to the less cumbersome milligram in the place of those remote fractions of a gramme which, though previously receiving official blessing, had no place in practical therapeutics.

I express my sincere thanks to Dr. P. M. F. Bishop for his careful revision of the chapter on Sex Hormones.

A. H. D.

LONDON, W. 1.

CONTENTS

PAGE
DEFINITIONS 1
PHARMACY 2
PHARMACEUTICAL PROCESSES 6
WEIGHTS, MEASURES, SYMBOLS 7
PHARMACOPŒIAL PREPARATIONS AND DOSES . . . 9
ADMINISTRATION OF DRUGS 26
PRESCRIBING 30
  DANGEROUS DRUGS ACTS AND POISONS RULES (1935) 35
PHARMACOLOGICAL AND THERAPEUTIC ACTIONS . . 36

PART I

Substances used chiefly for their Local Action

GROUP I. Demulcents—Emollients—Dusting Powders . 38
II. Carbohydrate Nutrients and Flavouring Agents 48
III. Bitters 52
IV. Volatile Oils and Cantharidin 55
V. Digestive Ferments 75
VI. Purgatives 76
VII. Astringents 96
VIII. Cholagogues 101
IX. Anthelmintics 103
X. Antiseptics 111
XI. Colouring Agents 136
XII. Substances whose Action is Physical . . 137
XIII. Dyes 139

PART II

Substances used chiefly for their General Action

GROUP I. Water, Chlorides, Urea and Suramin . . 142
II. Hydrates, Carbonates, Acetates and Citrates of Sodium and Potassium 148
III. Ammonium 153
IV. Saline Diuretics 155
V. Calcium and Barium 156
VI. Acids 162
VII. Charcoal 169
VIII. Carbon Dioxide and Oxygen 170
IX. Iodides and Iodine Compounds . . . 173
X. Bromides 177

PAGE

GROUP XI. Alcohols, Volatile Anæsthetics and Nitrous Oxide 181
Ethyl Alcohol—Tribromoethyl Alcohol—Chloroform—Ether—Ethyl Chloride—Vinyl Ether—Ethylene—Cyclopropane—Nitrous Oxide.

XII. Hypnotics 204
Halogen Derivatives—Aldehydes—Sulphones—Carbamates—Urea Derivatives—Alcohols.

XIII. Action of Drugs on Nervous System . . 222

XIV. Vegetable Drugs acting chiefly on Spinal Cord 261

XV. Vegetable Drugs acting chiefly on Autonomic Ganglia and Nerve Endings . . . 268

XVI. Nitrites 291

XVII. Antipyretics 295

XVIII. Cinchona Bark, Quinine, Quinidine, Pamaquine, Mepacrine 301

XIX. Salicin, Salicylates, Benzoin and Benzoates . 309

XX. Sulphonamides 316

XXI. Digitalis, Strophanthus, Ouabain and Squill . 335

XXII. Emetics and Expectorants 343

XXIII. Prussic Acid and Virginian Prune . . . 351

XXIV. Colchicum and Cinchophen 354

XXV. Vegetable Drugs acting on the Uterus . . 357

XXVI. The Heavy Metals 366
Lead — Silver — Gold — Zinc — Copper — Manganese—Aluminium—Iron—Mercury—Thallium—Radium—Thorium.

XXVII. The Metalloids 402
Bismuth—Arsenic—Antimony—Chromium—Phosphorus.

XXVIII. Hormone Preparations 419

XXIX. Ephedrine and Amphetamine . . . 457

XXX. Antitoxic Sera and Toxins . . . 460

XXXI. Vaccines 467

XXXII. Vitamins 474

XXXIII. Nucleic Acid and Nucleotides . . . 488

XXXIV. Anticoagulants 488

XXXV. Antibiotics 497

XXXVI. Insecticides 505

APPENDIX. LATIN PHRASES USED IN PRESCRIPTIONS . 508

INDEX 509

Abbreviations

Official substances are marked (**B.P.**).

Other drugs described in the British Pharmaceutical Codex are marked (**B.P.C.**).

Unofficial synonyms and trade names are indicated by the prefix *Unoff. Synonym* and *Tr. Name* respectively.

gr. = grain.
G. = gramme.
ml. = millilitre.
mg. = milligram.

MATERIA MEDICA

Materia Medica is so wide a term that it is difficult to define. It includes the following:

(*a*) **Materia Medica proper,** called Pharmacognosy. This is the knowledge of the natural history, physical characters, and chemical properties of drugs.

(*b*) **Pharmacy.** This is the science and art of the preparation and combination of drugs, so as to render them fit for administration.

(*c*) **Pharmacology.** This is the science which treats of the actions of drugs on the body both in health and disease. A subdivision of it is Pharmacodynamics, which is the science of the physiological action of drugs in health. The science which studies the effects of doses large enough to endanger life is **Toxicology.**

(*d*) **Therapeutics** is the science and art of alleviating or curing disease. Many authors do not include this under the term Materia Medica. Therapeutics is either—

(1) **Rational,** when we have sufficient knowledge of the disease and the pharmacological action of the remedy to know why it should be of benefit, *e.g.* The use of digitalis for auricular fibrillation.

(2) **Empirical,** when our knowledge is insufficient to tell us why the remedy is efficient, *e.g.* The use of salicylates for rheumatic fever.

Therapeutics ought not to be included in the term Materia Medica, for that treats only of drugs; but Therapeutics, properly speaking, is concerned with all means of alleviation.

General Therapeutics is a subdivision of Therapeutics; it is the science and art of alleviating disease by such remedies as are not drugs, *e.g.* diet, climate, baths, venesection, and cupping. In this work we shall consider only that part of Therapeutics which is concerned with drugs.

A Pharmacopœia is a book published by some authorized body, generally constituted by law. This book describes most of the drugs in common use, with directions for their preparation, identification, standardization and dosage. The pharmacopœias and the authorities publishing them differ in different countries. The **British Pharmacopœia** is published by the General Medical Council. The last appeared in 1948. As new drugs are discovered they are, if of sufficient use, included in new editions of the Pharmacopœia or in **Addenda** published from time to time. Everything contained in the Pharmacopœia is said to be "official." The abbreviation for "British Pharmacopœia" is "**B.P.**"

The Council of the Pharmaceutical Society of Great Britain publish "The British Pharmaceutical Codex," containing many preparations not in the British Pharmacopœia. The last appeared in 1934. When prescribed, **B.P.C.** should be put in a bracket after them.

MATERIA MEDICA PROPER

As much of this as the student need know will be mentioned under each drug.

PHARMACY

Pharmacy is for the most part carried out by the manufacturing and dispensing chemist. The medical student should, however, be acquainted with the simpler processes, as he may have to perform them. They are best learnt in the dispensary. An elementary knowledge of chemistry will enable him to understand most of the terms used in pharmacy, but the following should be noticed.

Alkaloids are bodies having the following characteristics:

1. They are the active nitrogenous principles of organic bodies.
2. They are compound ammonias: that is to say, one or more atoms of hydrogen in ammonia (NH_3) are replaced by various radicals.
3. They combine with acids to form crystalline salts without the production of water.
4. They are alkaline, turning red litmus paper blue.
5. A few are liquid, such as pilocarpine, coniine, nicotine, sparteine, lobeline. Liquid alkaloids nearly always contain only carbon, hydrogen, and nitrogen.
6. The solid ones are colourless, crystalline, and contain oxygen.
7. They are sparingly soluble in water, readily so in alcohol. Their salts are usually soluble in water.
8. The solutions of many are intensely bitter.
9. Most of them are closely related to pyridine, and some may be synthetically prepared from pyridine bases.

Names of alkaloids terminate in English in *-ine* (quinine), in Latin in *-ina* (quinina). Examples in B.P.: Atropine, Cocaine, &c.

Glucosides are crystalline bodies which when acted upon by acids, or chemical ferments (enzymes), split up into sugar (nearly always glucose) and other substances (alcohols, aldehydes, phenols, &c.), different in each case.

Example in B.P.: Digoxin. Many varieties of tannic acid exist in plants as Glucosides.

Saponins are a group of glucosides forming a clear solution in water, which froths on shaking, and may be used to emulsify oils and resins. Senega contains a powerful saponin.

Neutral Principles are indifferent proximate crystalline principles whose chemical characters have not been determined.

Example in B.P.: Aloinum.

Fixed Oils are ethereal salts formed from the higher fatty acids and the trihydric alcohol glycerin, $C_3H_5(OH)_3$. At ordinary temperatures they remain liquid. The usual fatty acids entering into the composition of fixed oils are oleic, palmitic, and stearic.

Example: Olive oil consists of a mixture of a combination of oleic acid ($C_{18}H_{34}O_2$) with glyceryl (C_3H_5) and palmitic acid ($C_{16}H_{32}O_2$) with glyceryl. That is to say, ordinary olive oil is a mixture of two oils having the formulæ $C_3H_5(C_{18}H_{33}O_2)_3$ and

$C_3H_5(C_{16}H_{31}O_2)_3$ respectively. When acted upon by caustic alkalies or metallic oxides fixed oils form soaps (oleates, palmitates, or stearates of metals) and glycerin. This process is called saponification,

e.g. $C_3H_5(C_{18}H_{33}O_2)_3 + 3NaHO = \underset{\text{Sodium Oleate}}{\underset{\text{Hard Soap}}{3NaC_{18}H_{33}O_2}} + \underset{\text{Glycerin}}{C_3H_5(OH)_3}.$

Fixed Oils are obtained from the fruits or seeds of plants, or from animal tissues, by expression or by boiling with water and skimming off the melted oil. When pure they usually are yellow, and float on water; they cause a greasy mark on paper. They are called fixed because they cannot be distilled without decomposition. They are soluble in ether or chloroform.

Liquid fixed oils in B.P. are Olea Amygdalæ, Lini, Morrhuæ, Olivæ, Ricini.

Fats are fixed oils which are solid at ordinary temperatures; if extracted by expression sufficient heat to melt them must be used.

Examples in B.P.: Oleum Theobromatis, Adeps.

Waxes are chiefly composed of fatty acids combined with monohydric alcohols homologous with methyl alcohol.

Volatile or Essential Oils only resemble fixed oils in being soluble in the same media. They do not leave a greasy mark on paper. They are mostly inflammable, and lighter than water. They are highly aromatic, and sufficiently soluble in water to impart their odour and taste to it. Most are prepared by distillation. Their composition varies. They contain Aldehydes (Cinnamic Aldehyde, in oil of cinnamon), Phenol derivatives (Eugenol, in oil of cloves), Esters or Ethereal Salts (Methyl Salicylate, in oil of wintergreen), Alcohols (Menthol, in oil of peppermint), or Ketones (Carvol, in oil of caraway), generally associated with Terpenes (*see* oil of turpentine) of varying composition, and which may be the chief constituent of the oil (*e.g.* the Terpenes in oils of turpentine).

Examples in B.P.: Olea Anethi, Anisi, Cinnamomi, Lavandulæ, &c.

Resins are among the products of oxidization of volatile oils. They are soluble in alkalies, forming resin soaps. They are insoluble in water but not in alcohol, therefore they may be prepared by extraction with alcohol and precipitation with water.

The B.P. resins are Colophonium and Resina Podophylli.

Oleo-resins are natural solutions of resins in volatile oils.

In B.P.C. Copaiba.

Balsams are mixtures of oleo-resins with benzoic acid or cinnamic acid, or with both.

Those in B.P. are Benzoinum, Balsamum Peruvianum, Balsamum Tolutanum, Styrax.

Gums are exudations from the stems of plants containing one or more of :

(*a*) Arabin or soluble gums, *e.g.* Acacia.
(*b*) Bassorin or partially soluble gums, *e.g.* Tragacantha.
(*c*) Cerasin or insoluble gum.
Solutions of gum are precipitated by alcohol.

Gum-resins are exudations from plants consisting of a mixture of gums and resins. When they are rubbed with water the gum dissolves, and the resin remains mechanically suspended in the solution.

The B.P. gum-resin is Myrrha.

An Emulsion is a mixture of a fat or resin and a liquid, or two immiscible liquids in which the solid or one of the liquids is in a finely divided state and is held in suspension in such a manner that the particles do not coalesce. When oil and water are shaken together the oil is broken up into globules of varying size which are dispersed throughout the liquid. On standing for a short time the globules coalesce and form a distinct layer. If a third substance of a saponaceous, mucilaginous or albuminous nature be introduced and the oil broken up into small uniform particles a permanent emulsion will result.

Acacia gum is frequently used to form emulsions.

It is incompatible with iron perchloride, borax and lead subacetate.

Emulsions are broken by acids, undue proportions of metallic salts and alcoholic liquids.

When a heavy powder, *e.g.* bismuth carbonate, is suspended in a viscous liquid the result is called a Suspension.

PHARMACEUTICAL PROCESSES

Many of these, as filtration, precipitation, &c., need no explanation, but the following require a few words :

Levigation consists in reducing a drug to a very fine powder by triturating it with a little water and drying the resulting paste.

Elutriation consists in diffusing an insoluble powder in water, letting the heavier part settle, then decanting the supernatant fluid. The heavier powder in this is allowed to settle, the fluid decanted, and so on until a fluid containing powder of the required fineness is obtained.

Lixiviation consists in the extraction with water of the soluble matter of the ashes of anything which has been ignited, the solution being called a " lye."

Maceration consists in leaving coarsely powdered solid organic substances in contact for some time, at the temperature of the atmosphere, with a liquid in a vessel which is frequently agitated. The resulting solution is poured off and added to the liquid obtained from the remaining substance by pressure. The whole may be concentrated by heat. Many extracts and tinctures are made by maceration.

Percolation is a process for obtaining the soluble constituents of a drug by the descent of a solvent through it. The drug to be percolated is first moistened and then evenly packed into a tall slightly conical vessel having an outlet at the lower end. The outlet is closed and the percolating fluid, or **menstruum,** is poured on to the drug and allowed to macerate for a time. The outlet is then opened and as the percolate drips out it is collected. The **Marc** is the material after its exhaustion by maceration or percolation. Many liquid extracts and tinctures of vegetable drugs are prepared by percolation.

Repercolation consists in using the liquid obtained by percolating a substance as the menstruum for percolating a second portion of the same substance and using the liquid from this second percolation as a menstruum for percolating a third portion of the same substance, and so on as often as may be desired.

Scaling. Scale preparations are made by drying concentrated solutions of drugs on glass plates. The solid left behind forms a thin film on the plate, and this film is broken up. Some preparations of iron are scale preparations.

Standardizing. The Pharmacopœia directs that certain preparations made from drugs shall be standardized—that is to say, shall be made to contain a certain fixed proportion of the chief active principle, *e.g.* Opium to make Tincture or Extract must contain not less than 9·5 per cent. of Morphine. (N.B.—1 per cent. expressed concretely in the metric system is 1 gramme in 100 millilitres ; in the British system, 1 grain in 110 minims.)

Biological Assay. When a drug is a definite chemical body, *e.g.* strychnine in nux vomica, preparations of it can be standardized by chemical means ; but when its activity is due to a body or bodies which the chemist cannot estimate quantitatively, the attempt is made to determine the strength of its preparations by observing the minimum fatal dose of each, when administered under similar conditions, to animals of the same species and weight. Or the drug may be standardized by observation of the degree of some striking physiological effect, *e.g.* preparations of pituitary extract may be standardized by observing their effect on the guinea-pig uterus.

Many drugs are now officially standardized by this means. Examples : Antitoxins, Hormones, Heparin, and Penicillin.

WEIGHTS. MEASURES. SYMBOLS

Imperial System

WEIGHTS (Apothecary)

Latin Name.	Symbol.	English Name.	Equivalent.
Granum	gr.	A grain.	
Scrupulus	℈	A scruple.	20 grains.
Drachma	ʒ	A drachm.	60 grains, 3 scruples.
Uncia	℥	An ounce.	480 grains, 8 drachms.

WEIGHTS (Avoirdupois)

Name.	Symbol.	Equivalent.
Grain	gr.	
Ounce	oz.	437·5 grains.
Pound	lb.	7000 grains, 16 ounces.

CAPACITY

Latin Name.	Symbol.	English Name.	Equivalent.
Minimum	♏	A minim.	
Fluid drachma	ʒ	A fluid drachm.	60 minims.
Fluiduncia	℥	A fluid ounce.	480 minims, 8 fluid drachms.
Octarius	O	A pint.	20 fluid ounces.

Occasionally ʒ and ℥ are written f ʒ and f ℥ when they stand for fluid drachms and fluid ounces.

The sign ℥ is sometimes used to represent oz. (437·5 gr.), but this is much to be deprecated.

Relations of Measures to Weights

1 minim is the measure at 16·7° C. (62° F.) of 0·971 grain of water.
1 fluid drachm ,, ,, 54·687 grains ,,
1 fluid ounce ,, ,, 437·5 ,, ,,
(the avoirdupois ounce).
1 pint ,, 8750·0 grains of water.

Percentage Solutions. The expression "per cent." is used in one of the three following meanings :—

Per cent. w/w = weight in weight.
,, ,, v/v = volume in volume.
,, ,, w/v = weight in volume.

The last, w/v, presents a difficulty when apothecary weights and measures are used, as 1 minim does not represent the volume of 1 grain of water but only 0·971 grain.

In other words, 100 grains of water measure 110 minims (strictly 109·7143) at 16·7° C.

Therefore a 1 per cent. w/v solution is 1 grain in 110 minims or 4·375 grains in 1 fluid ounce (480 m.).

From these figures the amounts for any quantity of a solution of any percentage strength can be calculated.

In the pharmacopœial description of the various proportions which several parts of a compound bear to one another, the word parts means parts by weight ; the term fluid parts signifies the volume of an equal number of parts of water.

Metric System. This, which is as follows, is official on the Continent and in the B.P. for the making of drugs and preparations, and, together with the Imperial, for doses.

N.B. The Pharmacopœia indicates dosage in grammes or fractions of a gramme. Quantities less than 0·1 G. are expressed as milligrams or fractions of a milligram. Fluid measures are in multiples or fractions of a millilitre.

WEIGHTS

1 milligramme (Mg.) = 0·001 G.
1 gramme (G.) = weight of 1 millilitre or ml. of distilled water.

MEASURES OF CAPACITY

1 litre = the vol. at 4° C. of 1000 G. (1 kilo.) of water.

N.B. 1 cubic centimetre (abbrev. c.c.) is approximately the same as one millilitre.

Approximate Equivalences Imperial and Metric

WEIGHTS

Imperial Grains.	Metric Gramme.
$\frac{1}{200}$	0·0003
$\frac{1}{100}$	0·0006
$\frac{1}{60}$	0·001
$\frac{1}{40}$	0·0015
$\frac{1}{30}$	0·002
$\frac{1}{16}$	0·004
$\frac{1}{6}$	0·01
1	0·06
3	0·2
5	0·3

Grains.	Grammes
15	1
45	3
60	4
150	10
180	12
240	16

VOLUMES

Minims.	Ml.
½	0·03
1	0·06
5	0·3
15	1
30	2
45	3
60	4
90	6

Fluid drachms.	Ml.
½	2
1	4
2	8
6	24
Fluid ounces.	**Ml.**
½	15
1	30
2	60
4	120

Domestic Measures

A TEA-SPOONFUL is rather over a fluid drachm. Usually it is 5 ml. nearly.

A DESSERT-SPOONFUL is about two fluid drachms.

A TABLE-SPOONFUL is about half a fluid ounce. Usually it is very nearly 15 ml.

A WINE-GLASSFUL is about one and a half to two fluid ounces.

A TEA-CUPFUL is about five fluid ounces.

A BREAKFAST-CUPFUL is about eight fluid ounces.

A TUMBLERFUL is about eleven fluid ounces.

A DROP is often taken as being about a minim, but drops vary so much in size that they should never be used for children nor as a measure of powerful drugs. For example, the number of drops in a fluid drachm of the United States syrup of acacia is 44, of water 60, of alcohol 146, of chloroform 250.

PHARMACOPŒIAL PREPARATIONS AND THEIR DOSES

Most drugs are not, in their natural state, fit for administration. They are either too bulky, too nauseous, or contain noxious principles. Preparations suitable for administration are there fore prepared from them according to "official" pharmacopœial directions. The Pharmacopœia states the doses of the various drugs and their preparations which may safely be given to an adult, but these doses are often not rigorously kept in prescribing. They vary with the purpose for which the drug is required and the age of the patient (*see* Prescribing). The following is an account of the compounding of the pharmacopœial preparations, the doses having been grouped to make them easy to learn. (The general procedure adopted in the preparation of antitoxic sera and vaccines is considered in the sections devoted to these substances.)

Aceta. Solutions of the active principles of the drug extracted from it by maceration or digestion with acetic acid (not vinegar). The **B.P.** contains one.

	Dose.
Acetum Scillæ	10—30 min. 0·6—2 ml.

Aquæ. (Waters.)

Aquæ Aromaticæ. These are aqueous fluids impregnated with some aromatic substance, usually a volatile oil. The **B.P.** contains two kinds—concentrated and distilled.

	Dose
Aqua Anethi Concentrata — Cinnamomi — — Menthæ Piperitæ —	5—15 min. 0·3—1 ml.

	Dose.
Aqua camphoræ — chloroformi	½ to 1 fl. oz. 15 to 30 ml.

Aqua Distillatæ. The **B.P.** gives directions for the preparation of the following unmedicated distilled waters.

Aqua Destillata — Pro Injectione.	No dose.

Collodia (collodions). Solutions of pyroxylin. When applied externally a protective film is formed owing to the rapid volatilization of the solvent. The **B.P.** contains one:

Collodium flexile.

Cremora. Creams are preparations having wax, glycerin, soft paraffin, or some similar substance as a basis, and used for external application. The **B.P.** contains

Cremor Penicillini
— — Sterilisatus

Emulsiones. An emulsion consists of two liquid phases, one of which is subdivided finely and dispersed in the other, the system being made more or less permanent by an emulsifying agent. The **B.P.** contains four :

Emulsio Chloroformi	Dose. 5—30 min.	0·3—2ml.
— Menthæ Piperitæ		
— Olei Morrhuæ	120—360 min.	8—24 ml.
— Paraffini Liquidi	¼—1 fl. oz.	8—30 ml.

Extracta. Concentrated preparations obtained by separating the soluble matter from vegetable or animal tissues by means of water, alcohol or some other suitable solvent. The liquid so obtained is concentrated by evaporation to make a Liquid Extract, or evaporated to dryness, or nearly to dryness to form a Solid Extract. Solid extracts may be dry powders or soft viscous masses known as Soft Extracts.

Extracts may be classified as follows :—

1. Solid Extracts.

(*a*) *Dry Extracts.* Drugs are treated with water, or alcohol, and the resulting liquid evaporated to dryness. The residue is reduced to a fine powder or granules.

(*b*) *Soft Extracts.* The evaporation is stopped just short of dryness to produce an extract of a soft pilular consistence, *e.g.* Ext. Gentian.

2. Liquid Extracts.

These are aqueous or alcoholic extracts evaporated to form a concentrated syrupy liquid. They are made by maceration or percolation processes.

There are three extracts in the **B.P.** which do not belong to any of the foregoing groups. Ext. Filicis is a thick oily liquid which is obtained by percolating the drug with Ether and allowing the solvent to evaporate. Ext. Malti, a thick viscid liquid, is a food adjunct rather than a drug ; and Ext. Malti cum Ol.

Morrhuæ is an emulsion in which the malt extract is the emulsifying agent.

Solid Extracts.

	Dose.
Extractum Colchici Siccum	$\frac{1}{6}$—$\frac{1}{2}$ gr. 10—30 mg.
— Belladonæ Siccum	$\frac{1}{4}$–1 gr. 15—60 mg.
— Hyoscyami Siccum	
— Nucis Vomicæ Siccum	
— Stramonii Siccum	
— Cascaræ Sagradæ Siccum	2–8 gr. 0·12—0·5 G.
— Colocynthidis Co.	
— Glycyrrhizæ	10—30 gr. 0·6—2 G.
— Fellis Bovini	5–15 gr. 0·3—1 G.
— Krameriæ Siccum	
— Hamamelidis Siccum	No dose

Liquid Extracts.

Extractum Belladonæ Liquidum	No dose
— Ipecacuanhæ Liquidum	$\frac{1}{2}$ to 2 min. 0·03—0·12 ml. 10—30 min. 0·6—2 ml. as emetic

Liquid Extracts.

	Dose.
Extractum Stramonii Liquidum	$\frac{1}{2}$—3 min. 0·03—0·2 ml.
— Quillaiæ Liquidum	No dose
— Nucis Vomicæ Liquidum	1—3 min. 0·06—0·2 ml.
— Colchici Liquidum	No dose
— Hyoscyami Liquidum	3—6 min. 0·2—0·4 ml.
— Senegæ Liquidum	5–15 min. 0·3—1 ml.
— Ergotæ Liquidum	10—20 min. 0·6—1·2 ml.
— Sennæ Liquidum	10–30 min. 0·6—2 ml.
— Cascaræ Sagradæ Liquidum	30—60 min. 2—4 ml.
— Glycyrrhizæ Liquidum	
— Hamamelidis Liquidum	No dose
— Filicis	45–90 min. 3—6 ml.
— Malti c. Ol. Morrh.	60 min.—1 fl. oz. 4—30 ml.
— Malti	
— Hepatis Liquidum	1 fl. oz. 30 ml.

Glycerina. Solutions of drugs in glycerin. They are liquid preparations, except Glycerinum Amyli, which is a jelly. The **B.P.** contains five :

Glycerinum Acidi Borici **— Acidi Tannici** **— Boracis**	No dose	**Glycerinum Amyli** **— Phenolis**	**No dose**

Infusa. Concentrated infusions which are made by treating the substance to be extracted with alcohol and water. Infusions are prepared from these by the addition of distilled water. The former are relatively stable ; the latter should be dispensed within twelve hours of preparation. The **B.P.** contains seven concentrated infusions and seven fresh infusions :

	Dose.		*Dose.*
Infusum Aurantii Concentratum — Calumbæ — — Caryophylli — — Gentianæ Compositum — — Quassiæ — — Senegæ —	30—60 min. 2—4 ml.	Infusum Aurantii — Calumbæ — Caryophylli — Gentianæ Compositum — Quassiæ — Senegæ	$\frac{1}{2}$—1 fl. oz. 15—30 ml.
— Sennæ —	30—120 min. 2—8 ml.	Infusum Sennæ	$\frac{1}{2}$—2 fl. ozs. 15—60 ml.

Injectiones. The official injections are :

	Dose.		*Dose.*
Injectio Æthanolaminæ Oleatis	30—75 min. 2—5 ml.	Injectio Antimonii et Potassii Tartratis — — — Sodii —	$\frac{1}{2}$—2 gr. 30—120 mg.
— Adrenalinæ	2—8 min. 0·12—0·5 ml.	— Apomorphinæ Hydrochloridi	$\frac{1}{32}$—$\frac{1}{8}$ gr. 2—8 mg.
— Amethocainæ Hydrochloridi	No dose		
— Aneurinæ — Hydrochloridi	$\frac{1}{6}$—$\frac{1}{2}$ gr. 10—30 mg.	— Atropinæ Sulphatis	$\frac{1}{240}$—$\frac{1}{60}$ gr. 0·25—1 mg.

	Dose.
Injectio Bismuthi	8—15 min. 0·5—1 ml.
— Bismuthi Oxychloridi	15—30 min. 1—2 ml.
— Bismuthi Salicylatis	10—20 min. 0·6—1·2 ml.
— Bismuthi et Sodii Tartratis	1—3 gr. 60—200 mg.
— Caffeinæ et Sodii Benzoatis	2—5 gr. 0·12—0·3 G.
— Calcii Gluconatis	150—300 min. 10—20 ml.
— Carbacholi	$\frac{1}{240}$—$\frac{1}{120}$ gr. 0·25—0·5 mg.
— Deoxycortoni Acetatis	$\frac{1}{30}$—$\frac{1}{6}$ gr. 2—10 mg
— Dextrosi	No dose
— Digoxini	150—300 min. 10—20 ml. i.v.
— Diodoni	300 min. 20 ml. for adult, i.v.
— Emetinæ Hydrochloridi	$\frac{1}{2}$—1 gr. 30—60 mg.
— Ergometrinæ Maleatis	$\frac{1}{240}$—$\frac{1}{120}$ gr. 0·25—0·5 mg. i.m. $\frac{1}{480}$—$\frac{1}{240}$ gr. 0·125—0·25 mg. i.v.

	Dose.
Injectio Gonadotrophini Chorionici	100—500 units
— — Serici	200—1,000 units
— Heparini	6,000—12,000 units (i.v.)
— Hexobarbitoni Sodii	3—15 gr. 0·2—1 G.
— Histaminæ Phosphatis Acidi	$\frac{1}{120}$—$\frac{1}{60}$ gr. 0·5—1 mg.
— Hyoscinæ Hydrobromidi	$\frac{1}{200}$—$\frac{1}{100}$ gr. 0·3—0·6 mg.
— Insulini	20 units per ml.
— — Protaminati cum Zinco	40 units per ml.
— Iodoxyli	150—225 gr. 10—15 G. i.v.
— Leptazoli	8—15 min. 0·5—1 ml.
— Menaphthoni	$\frac{1}{60}$—$\frac{1}{12}$ gr. 1—5 mg. i.m.
— Mepacrinæ Methanosulphonatis	$1\frac{1}{2}$—5 gr. 0·1—0·3 G. i.m.
— Mersalyli	8—30 min. 0·5—2 ml.
— Morphinæ et Atropinæ	8—15 min. 0·5—1 ml.
— — Sulphatis	$\frac{1}{8}$—$\frac{1}{8}$ gr. 8—20 mg.
— Neoarsphenaminæ	$2\frac{1}{2}$—10 gr. 0·15—O.6 G.

	Dose.
Injectio Neostigminæ Methylsulphatis	$\frac{1}{120}$—$\frac{1}{30}$ gr. 0·5—2 mg.
— Nikethamidi	No dose
— Œstradiolis Dipropionatis	$\frac{1}{60}$—$\frac{1}{12}$ gr. 1—5 mg.
— — Monobenzoatis	
— Olei Hydnocarpi	30—75 min. 2—5 ml.
— — — Æthylici	
— Ouabaini	$\frac{1}{500}$—$\frac{1}{240}$ gr. 0·12—0·25 mg.
— Oxytocini	5—10 units
— Penicillini	50,000 units per ml.
— — Oleosa	125,000 units per ml.
— Procainæ et Adrenalinæ	No dose
— Procainæ et Adrenalinæ Mitis	No dose
— Pethidinæ Hydrochloridi	$\frac{2}{5}$—$1\frac{1}{2}$ gr. 25—100 mg.
— Phenobarbitoni Sodii	1—3 gr. 60—200 mg.
— Physostigminæ Salicylatis	$\frac{1}{100}$—$\frac{1}{50}$ gr. 0·6—1·2 mg.
— Picrotoxini	$\frac{1}{100}$—$\frac{1}{20}$ 0·6—3 mg.
— Pituitarii Posterioris	2—5 units

	Dose.
Injectio Progesteroin	$\frac{1}{30}$—$\frac{1}{3}$ gr. 2—20 mg.
— Quininæ Dihydrochloridi	5—10 gr. 0·3—0·6 G.
— Quininæ et Urethani	8—75 min. 0·5—5 ml.
— Sodii Aurothiomalatis	$\frac{1}{6}$ gr. increasing to $1\frac{1}{2}$ gr. weekly 10 mg. increasing to 100 mg. weekly
— — Bicarbonatis (5 per cent.)	No dose
— — Citratis Anticoagulans (2·5 per cent.)	
— — — cum Dextroso	
— — Lactatis Composita	
— Sodii Chloridi	
— — — Composita	
— Stibopheni	25—75 min. 1·5—5 ml.
— Strychninæ Hydrochloridi	$\frac{1}{30}$—$\frac{1}{16}$ gr. 2—4 mg.
— Sulphadiazinæ Sodii	8—30 gr. 0·5—2 G. i.v.
— Sulpharsphenaminæ	$1\frac{1}{2}$—10 gr. 0·1—0·6 G.

	Dose.
Injectio Sulphathiazoli Sodii	8—30 gr. 0·5—2 G. i.v.
— Suramini	15—30 gr. 1—2 G.
— Testosteroni Propionatis	$\frac{1}{12}$—$\frac{2}{5}$ gr. 5—25 mg.
Injectio Theophyllinæ cum Æthylenediamina	1½—8 gr. 0·1—0·5 G.
— Thiopentoni Sodii	1½—8 gr. 0·1—0·5 G.
— Tryparsamidi	15—30 gr. 1—2 G.
— Vasopressini	5—15 Units.

Lamellæ. Small thin discs made with gelatin and glycerin, and used to drop into the eye. The **B.P.** contains four :

Lamella Atropinæ (each contains $\frac{1}{5000}$ gr. (0·013 mg.) atropine sulphate).

Lamella Cocainæ (each contains $\frac{1}{50}$ gr. (1·3 mg.) cocaine hydrochloride).

Lamella Homatropinæ (each contains $\frac{1}{100}$ gr. (0·65 mg.) of homatropine hydrobromide).

Lamella Physostigminæ (each contains $\frac{1}{1000}$ gr. (0·065 mg.) physostigmine salicylate).

Linimenta. Liniments or embrocations are applications of an oily or spirituous consistence, all of which are intended to be rubbed into the skin except Lin. Aconiti, which is painted on it. Most contain camphor, some contain olive oil, most contain alcohol. The **B.P.** contains six :

Linimentum Aconiti
— Belladonnæ
— Camphoræ
— — Ammoniatum
Linimentum Saponis
— Terebinthinæ

Liquores. Solutions generally of definite chemical bodies, and in which the solvent is usually distilled water or alcohol. In many cases these are the only constituents. The few exceptions can be found by reference to individual Liquors.

The following are the doses of Liquors

	Dose.
Liquor Vitamini D Concentratus	1½—6 min. 0·1—0·4 ml.
— Vitamini A Concentratus — Vitaminorum A et D Concentratus	1—10 min. 0·06—0·6 ml.
— Æthylis Nitritis Concentratus — Arsenicalis	2—8 min. 0·12—0·5 ml.
— Strychninæ Hydrochloridi	3—12 min. 0·2—0·8 ml.
— Ferri Perchloridi — Iodi Aquosus	5—15 min. 0·3—1 ml.
— Iodi Mitis — Morphinæ Hydrochloridi	5—30 min. 0·3—2 ml.
Liquor Adrenalinæ Hydrochloridi — Ammoniæ Dilutus — — Fortis — Chloroxylenolis — Cresolis Saponatus — Formaldehydi — Hydrogenii Peroxidi	No dose

	Dose.
Liquor Ammonii Acetatis Fortis	15—60 min. 1—4 ml.
— Hydrargyri Perchloridi	30—60 min. 2—4 ml.
— Ammonii Acetatis Dilutus	¼—1 fl. oz. 8—30 ml.
— Magnesii Bicarbonatis	1—2 fl. oz. 30—60 ml.
— Calcii Hydroxidi	1—4 fl. oz. 30—120 ml.
— Calciferolis prophylactic (daily) for infant	1000 to 4000 Units
— therapeutic (daily)	2000 to 20,000 Units
Liquor Iodi Fortis — Picis Carbonis — Plumbi Subacetatis Dilutus — — — Fortis — Potassii Hydroxidi — Sodæ Chlorinatæ Chirurgicalis	No dose

Lotiones. Aqueous mixtures for external use, generally applied on lint, or washed on the part. The **B.P.** contains one :

Lotio Calaminæ.

Mella. Mixtures of some substance with purified honey. The **B.P.** contains only one.

Mel Depuratum.

Misturæ. Liquid preparations consisting of more than one drug dissolved in water or diffused in some thick fluid. The mixture is usually flavoured, and is for internal administration.

The **B.P.** now contains only two :

		Dose.
Mistura Magnesii Hydroxidi	60—240 min.	4—16 ml.
— Sennæ Composita	1—2 fl. oz.	30—60 ml.

Mucilagines. Mucilages are aqueous, viscid solutions or partial solutions of gum used for suspending insoluble substances. The **B.P.** contains two :

Mucilago Acaciæ and Mucilago Tragacanthæ.

Oculenta. Ointments for the eye made by the incorporation of the drug in a mixture of yellow soft paraffin and wool fat. The **B.P.** contains seven :

Oculentum Atropinæ, 0·25 per cent. ; Atropinæ c. Hydrargyri Oxido, 0·125 and 1 per cent. ; Cocainæ, 0·25 per cent. ; Hydrargyri Oxidi, 1 per cent. ; Hyoscinæ, 0·125 per cent. ; Penicillini, 1000 Units per G. ; Physostigminæ, 0·125 per cent.

Olea. The oils in the Pharmacopœia are obtained by distillation or by expression. The **B.P.** olea are :

	Dose.
Oleum Anethi — Anisi — Cajuputi — Cari — Caryophylli — Cinnamomi — Coriandri — Eucalypti — Menthæ Piperitæ — Myristicæ	1—3 min. 0·06—0·2 ml.
— Hippoglossi	1—8 min. 0·06—0·5 ml.
— Terebinthinæ	3–10 min. 0·2—0·6 ml.

	Dose.
Oleum Chenopodii	3—15 min. 0·2—1 ml.
Oleum Hydnocarpi Oleum Hydnocarpi Æthylicum	5—15 min. increasing gradually to 60 min. 0·3—1 ml. increasing gradually to 4 ml.

	Dose.
Oleum Morrhuæ	60—180 min. 4—12 ml.
— Ricini	60—240 min. 4—16 ml.
— Amygdalæ — Lini — Olivæ	½—1 fl. oz. 15—30 ml.

	Dose.
— Amygdalæ Volatile Purificatum — Arachis — Cadinum — Gossypii Seminis — Iodisatum — Limonis — Lavandulæ — Rosmarini — Sesami — Theobromatis	No dose

Oxymella. Oxymels are preparations containing honey and acetic acid. Besides oxymel the **B.P.** contains only one :

Oxymel Scillæ. *Dose* 30—60 min. 2—4 ml.

Pasta. A paste is a preparation to be applied externally.

The **B.P.** has one : Pasta Zinci Oxidi Composita.

Pilulæ. Solid spherical bodies containing medicinal agents, and intended to be swallowed whole. In order that they may not possess a disagreeable taste, they are often varnished or sugar-coated. Unless the constituents are very heavy, each pill should not exceed 5 grains in weight. All pills are useless unless so made that they will dissolve in the gastro-intestinal canal. If it is required that they should not be acted upon until they reach the intestine, they should be coated with keratin.

The **B.P.** contains :—

	Dose.
Pilula Aloes — Colocynthidis et Hyoscyami — Hydrargyri — Rhei Composita	4—8 gr. 0·25—0·5 G.
— Ferri Carbonatis	5—30 gr. 0·3—2 G.

Pulveres. The **B.P.** contains :—

	Strength.	*Dose.*
Belladonna Pulverata	. 0·3 per cent. alkaloids	½—3 gr. 0·03—0·2 G.
Digitalis Pulverata .	. 10 units of activity per G.	½—1½ gr. 0·03—0·1 G. Single 3—10 gr. 0·2—0·6 G.
Ergota Præparata .	. 0·1 per cent. alkaloids	5—15 gr. 0·3—1 G.
Ipecacuanha Pulverata	. 2 per cent. alkaloids	½—2 gr. 0·03—0·12 G. *Emetic.* 15—30 gr. 1—2 G.
Jalapa Pulverata .	. 10 per cent. resin	5—20 gr. 0·3—1·2 G.
Nux Vomica Pulverata	. 1·2 per cent. strychnine	1—4 gr. 0·06—0·25 G.
Opium Pulveratum .	. 10 per cent. morphine	½—3 gr. 0·03—0·2 G.

Compound Powders. Mixtures of two or more finely powdered drugs. The **B.P.** contains nine :

	Dose.
Pulvis Ipecacuanhæ et Opii	5—10 gr. 0·3—0·6 G.
— Cretæ Aromaticus — — — cum Opio — Rhei Co. — Tragacanthæ Co.	10—60 gr. 0·6—4 G.
— Glycyrrhizæ Compositus	60—120 gr. 4—8 G.
— Effervescens Compositus (Seidlitz Powder, *q.v.*).	

Spiritus. Spirits are either simple or complex. Simple Spirits are solutions (which frequently become turbid on the addition of water, owing to the separation of the substance dissolved) in alcohol (90 per cent.) of—

(*a*) A volatile oil :
Spiritus Cajuputi. Spiritus Menthæ Piperitæ.
The strength of these is 1 in 10, and the dose 5—30 min. 0·3—2 ml.

(*b*) Of camphor :
Spiritus Camphoræ. *Strength* 1 in 10. *Dose* 5—30 min. 0.3—2 ml.

(*c*) Of chloroform :
Spiritus Chloroformi. *Strength* 1 in 20. *Dose* 5—30 min. 0·3—2 ml.

(*d*) Of ether :
Spiritus Ætheris. *Strength* 1 in 3. *Dose* 15—60 min. 1—4 ml.

(*e*) Of wood naphtha :
Spiritus Methylatus Industrialis. *Strength* 1 in 20. No dose.

Complex Spirits are of varying composition. They are prepared by distillation. The **B.P.** now contains two :

	Dose.
Spiritus Ætheris Nitrosi	15—60 min.
— Ammoniæ Aromaticus	1—4 ml.

NOTE.—Sp. is in English a common abbreviation for Spiritus. In French it is the abbreviation for Syrup.

Suppositoria. Suppositories are conical solid bodies containing active drugs for introduction into the rectum or vagina. Each is made to weigh 1 G. The basis of all is oil of theobroma, except Sup. Glycerini.

The **B.P.** contains ten, viz. Suppositoria Acidi Tannici, 3 gr. (0·2 G.) ; Sup. Belladonnæ, $\frac{1}{60}$ gr. (1 mg.) ; Sup. Bismuth Subgallatis, 5 gr. (0·3 G.) ; Sup. Cocainæ, ¼ gr. (15 mg.) ; Sup. Hamamelidis, 3 gr. (0·2 G.) ; Sup. Hamamelidis et Zinci Oxidi, 3 gr. (0·2 G.) and 10 gr. (0·6 G.) ; Sup. Iodoformi, 3 gr. (0·2 G) ; Sup. Morphinæ, ¼ gr. (15 mg.) ; Sup. Phenolis, 1 gr. (60 mg.) ; Sup. Glycerini, 70 per cent. in gelatin.

Syrupi. Syrups are saturated or nearly saturated solutions of sugar containing flavouring, colouring or therapeutically active substances.

Example : Sy. Aurantii. The dose of all is 30—120 min (2—8 ml.) except Sy. Scillæ, of which it is 30—60 min. (2—4 ml.) Syrupus Glucosi Liquidi has no dose.

Tabellæ. Tablets are solid discs prepared by compressing or moulding a drug, or a mixture of drugs. The **B.P.** contains the following tablets :—

	Content.
Tabellæ Acetomenaphthoni	$\frac{1}{12}$ gr.—5 mg.
— Acidi Acetylsalicylici	5 gr.—0·3 G.
— — — cum Ipecacuanha et Opio	2½ gr.—0·162 G. aspirin and 2½ gr.—0·162 G. Dover's powder
— — — et Phenacetini	3½ gr.—0·22 G. aspirin and 2½ gr.—0·16 G. phenacetin

	Content.
Tabellæ Acidi Ascorbici	$\frac{4}{5}$ gr.—50 mg.
— — Nicotinici	$\frac{4}{5}$ gr.—50 mg.
— Æthisteroni	$\frac{1}{12}$ gr.—5 mg.
— Aneurinæ Hydrochloridi	$\frac{1}{60}$ gr.—1 mg.
— Atropinæ Sulphatis	$\frac{1}{100}$ gr.—0·6 mg.
— Barbitoni	5 gr.—0·3 G.
— — Sodii	5 gr.—0·3 G.
— Calcii Lactatis	5 gr.—0·3 G.
— Codeinæ Compositæ	4 gr.—0·26 G. each of aspirin and phenacetin, and $\frac{1}{8}$ gr.—8 mg. codeine phosphate
— — Phosphatis	$\frac{1}{2}$ gr.—30 mg.
— Dienœstrolis	$\frac{1}{600}$ gr.—0·1 mg.
— Digitalis Præparatæ	1 gr.—60 mg.
— Digoxini	$\frac{1}{240}$ gr.—0·25 mg.
— Ephedrinæ Hydrochloridi	$\frac{1}{2}$ gr.—30 mg.
— Ergotæ Præparatæ	$2\frac{1}{2}$ gr.—0·15 G.
— Glycerylis Trinitratis	$\frac{1}{130}$ gr.—0·5 mg.
— Hexœstrolis	$\frac{1}{60}$ gr.—1 mg.
— Hydrargyri cum Creta	1 gr.—60 mg.
— — Subchloridi	1 gr.—60 mg.
— Ipecacuanhæ et Opii	5 gr.—0·3 G.
— Mepacrinæ Hydrochloridi	$1\frac{1}{2}$ gr.—0·1 G.
— Methyltestosteroni	$\frac{1}{12}$ gr.—5 mg.
— Methylthiouracili	$1\frac{1}{2}$ gr.—0·1 G.
— Nicotinamidi	$\frac{4}{5}$ gr.—50 mg.
— Œstroni	$\frac{1}{60}$ gr.—1 mg.
— Phenacetini	5 gr.—0·3 G.
— Phenazoni	5 gr.—0·3 G.
— Phenobarbitoni	$\frac{1}{2}$ gr.—30 mg.
— — Sodii	$\frac{1}{2}$ gr.—30 mg.
— Phenolphthaleini	2 gr.—120 mg.
— Potassii Bromidi	5 gr.—0·3 G.
— — Chloratis	5 gr.—0·3 G.
— Quininæ Bisulphatis	5 gr.—0·3 G.
— — Hydrochloridi	5 gr.—0·3 G.
— Sodii Bicarbonatis Compositæ	5 gr.—0·3 G.
— — Citratis	2 gr.—120 mg.
— — Salicylatis	5 gr.—0·3 G.
— Stilbœstrolis	$\frac{1}{130}$ gr.—0·5 mg.
— Succinylsulphathiazoli	8 gr.—0·5 G.
— Sulphadiazinæ	8 gr.—0·5 G.
— Sulphaguanidinæ	8 gr.—0·5 G.
— Sulphanilamidi	8 gr.—0·5 G.
— Sulphathiazoli	8 gr.—0·5 G.
— Thiouracili	$1\frac{1}{2}$ gr.—0·1 G.
— Thyroidei	$\frac{1}{2}$ gr.—30 mg.

N.B.—The number of tablets to be given must be determined according to the dose of the active ingredient, or ingredients.

Tincturæ. Tinctures are solutions of the active principles of drugs in alcohol. They are closely allied to spirits, from which most of them differ in their mode of preparation. They are prepared by—

(*a*) Maceration.
(*b*) Percolation.
(*c*) Dilution of some more concentrated preparation.

The term tincture is no longer applied to simple alcoholic solutions of chemical substances, and for this reason the familiar tinctures of iodine are now to be found under Liquors.

	Dose.
Tinctura Strophanthi	2–5 min. 0·12—0·3 ml.
— Zingiberis Fortis	5—10 min. 0·3—0·6 ml.
— Belladonnæ	5—15 min. 0·3—1 ml.
— Capsici	
— Colchici	
— Digitalis	5—15 min. 0·3—1 ml.
— Opii	5—30 min. 0·3—2 ml.
— Scillæ	
— Stramonii	
— Ipecacuanhæ	10—30 min. 0·6—2 ml. as emetic ½—1 fl. oz. 15—30 ml. emetic
Tinctura Nucis Vomicæ	10—30 min. 0·6--2 ml.
— Aurantii	30—60 min. 2—4 ml.
— Calumbæ	
— Opii Camphorata	
— Cardomomi Co.	
— Catechu	
— Gentianæ Co.	
— Hyoscyami	
— Limonis	
— Myrrhæ	
— Quassiæ	
— Rhei Co.	
— Senegæ	
— Tolutana	
— Valerianæ Ammoniata	
— Zingiberis Mitis	
— Benzoini Co.	No dose
— Cocci	

Trochisci. Lozenges or Troches are small flattened cakes prepared from a basis of sugar and acacia, suitably flavoured and combined with medicaments usually intended for a prolonged local action on the mucous surfaces of the mouth and throat. They should be sucked slowly

The **B.P.** contains seven ·

Troch. Acidi Tannici (½ gr.) ; Bismuthi Co. (2¼ gr.) ; Krameriæ (1 gr.) ; Krameriæ et Cocainæ (1 gr. and $\frac{1}{20}$ gr.) ; Morphinæ et Ipecacuanhæ ($\frac{1}{32}$ gr. and $\frac{1}{10}$ gr.) ; Penicillini (500 units) ; Phenolis (½ gr.).

Unguenta. Ointments are semi-solid preparations consisting of a fatty substance mixed with an active drug. They are spread over the skin, or may be rubbed into it. They are only intended for external use. The basis may be either soft paraffin, lard or wool-fat, sometimes combined with hard paraffin, wax, olive oil or spermaceti.

Benzoinated lard is often used, as it is less liable to turn rancid than plain lard.

The drug, if insoluble in the base, should be in the finest possible state of division and be evenly distributed throughout. When it is required that the active ingredient should be absorbed, lard, which melts at about the temperature of the body, or hydrous wool-fat, is the best basis ; when the ointment is required for sores paraffin is a good basis, as it only softens a little at the temperature of the body.

In hot countries if the ointment would otherwise be too soft, the basis may be replaced by benzoinated lard, prepared suet, yellow beeswax or white beeswax.

The following NON-PHARMACOPŒIAL PREPARATIONS are used :

Ampullæ. Glass containers for solutions intended for injection.

Buginaria. Bougies are solid cylinders impregnated with various drugs, and used for introduction into the ear (called aurinaria), nose (called buginaria), or urethra. They are made either of gelatin (to be dipped in warm water before use) or oil of theobroma (to be dipped in oil before use). Those for the urethra are made in six sizes, varying from $\frac{1}{8}$ to $\frac{5}{16}$ inch in diameter.

Cachets, made of wafer paper, consist of two watch-glass-shaped halves. The drug is enclosed between them, and they adhere when moistened. The cachet is slightly moistened, put in the back of the mouth, and quickly washed down with a little water. This is an excellent way of giving drugs which are either nauseous or difficult of solution or suspension. Cachets are commonly used for antipyrin ; bismuth salts ; guaiacol carbonate ; phenacetin ; quinine salts ; aspirin, salol, and other salicylates ; sulphonal, trional, and veronal.

Capsulæ. Hard capsules of gelatin are used in the same way as cachets. Soft capsules are very useful for nauseous oils.

Cerata are ointments containing wax. They are official in the United States Pharmacopœia.

Collunaria. Fluids used as nasal douches.

Collyria. Fluids used as eye washes, isotonic with lachrymal secretion.

Confectiones (Syn. electuaries, boluses, conserves). Powders made into a paste with sugar or honey, of such a consistency that the powder does not separate, but the mass can be swallowed.

Emplastra. Plasters are preparations composed of resinous and adhesive substances, sometimes in conjunction with one or more active drugs, intended to adhere to the skin when applied in a thin layer spread on cloth, sheepskin leather or other fabric.

Enemata (enemas or clysters). Liquid preparations intended for injection into the rectum. When their object is to empty the bowel they are large in bulk (10 to 20 fl. oz.) ; when it is wished that they should be retained they are usually smaller in bulk. After injection a towel may be pressed against the anus. Mucilage made with starch (*see* Starch) is a good basis.

Essentiæ (essences). Solutions of volatile oils in rectified spirit, usually of a strength of 1 in 5.

Fomenta. Fomentations consist of flannels wrung out in hot water, to which drugs may or may not have been added.

Gargarisma. Aqueous solutions used for gargling.

Granulæ Effervescentes. Effervescent granules consist of citric and tartaric acids and sodium bicarbonate for purposes of effervescence when introduced into water. To these constituents is added the main pharmacological principle.

Guttæ. Fluid preparations to be dropped into the eye.

Haustus. A draught. This term is used when only a single dose of a fluid preparation is required.

Insufflationes. Powders for blowing into the throat and larynx.

Lincti. A linctus. This has honey, treacle, or some other thick substance as a basis. It is to be swallowed slowly, being retained some time in the mouth.

Nebulæ. Solutions intended to be sprayed into the throat by means of an atomizer.

Pastilli. Pastils are lozenges having glyco-gelatin as a basis used for applying medicaments to the throat and mouth.

Perles are small gelatin capsules.

Pessi. Pessaries are solid preparations made like suppositories, and introduced into the vagina.

Pigmenta. Paints are liquid preparations suitable for application to the skin or mucous membranes by means of a brush.

Vapores. Inhalations are preparations arranged for the inhalation of volatile drugs.

Vina. Wines are weak tinctures, the drug being extracted as a rule with sherry.

ADMINISTRATION OF DRUGS

MODES OF ADMINISTRATION OF DRUGS

(*a*) **Into the blood-vessels** by injection. This method is used for (1) the administration of drugs which are too irritating for introduction by alternative routes ; (2) restoration of blood volume, *e.g.* saline solution in shock ; (3) obtaining rapid results in emergencies ; (4) the treatment of diseased conditions of the veins, *e.g.* quinine for varices ; (5) the administration of substances which by their concentration in certain organs are a direct aid to diagnosis, *e.g.* iodophthalein. A specialized procedure for delivery of drugs or restorative fluids (*e.g.* blood) into the circulation consists of the introduction of a wide-bore needle into the marrow of the **sternum.** This is useful when veins are too small or collapsed, or when operations are being carried out on the head and neck. Injection fluid should be administered slowly and at body heat.

(*b*) **Into the subcutaneous tissues** by hypodermic injection. The advantage of this method is that the drug is surely and quickly absorbed. The fluid used must not contain solid particles, nor be irritating, or abscesses will result ; it must be aseptic. The bulk injected should, if possible, be about five minims. For injections that are not in constant use it is advisable to keep the drugs in the form of lamellæ, and to dissolve one in a few minims of water as required. The subcutaneous **implantation** of pellets of certain hormones is often carried out with the object of ensuring prolonged absorption of the drug into the blood.

(*c*) **Into muscles.** Intramuscular administration is used for (1) obtaining effects more quickly than is possible from subcutaneous injection ; (2) treatment by insoluble drugs where prolonged action is desired, *e.g.* mercury and bismuth, and where alternative routes are useless or painful.

(*d*) **Into serous cavities** by injection. This method is rarely used in man except when the object is to wash out, with saline solution, a serous cavity, as the pleura, or to produce adhesive inflammation, as in the injection of irritants into the tunica vaginalis.

(*e*) **Into mucous cavities.** Drugs are most frequently given by the **mouth**, to be absorbed from the mucous membrane of the stomach or intestines, but the rate of absorption is much slower than from the subcutaneous tissue, and will depend upon whether the drug is readily soluble in the gastro-intestinal secretions, and whether it is given on an empty stomach, in which case it will be quickly absorbed ; or on a full one, when it will be slowly absorbed.

Posterior pituitary extract is taken into the **nose** in the form of snuff in the treatment of diabetes insipidus. The drug is partly absorbed through the mucosa. Ease of repeated self-administration is the justification of this route.

Drugs are sometimes given by the **rectum**—in a solid form as **suppositories**, in a liquid form as **enemata** or clysters ; but they are neither dissolved nor absorbed here so quickly as in the upper part of the gastro-intestinal canal.

For local effects they may be given by the **urethra** or **vagina** (**injections, bougies, pessaries**), or by the **respiratory passages** (**inhalations, cigarettes, sprays,** or **nebulæ** for **inhaling**) ; **insufflations** for blowing into the throat and larynx ; **pigmenta, gargles, lozenges,** for a local effect on the mouth and pharynx ; **nasal douches** for the nose. Sometimes volatile drugs, as chloroform or amyl nitrite, are inhaled for their general effect.

(*f*) **By the skin.** Some drugs may be absorbed from the skin if mixed with fatty substances and rubbed in, *e.g.* mercury. They are chiefly applied, however, as ointments, plasters, &c., for their local effect.

Cataphoresis or **Ionization** is a means of introducing drugs through the skin. A large suitable pad soaked in a solution of the drug forms one pole of a galvanic battery. It is placed on the skin over the part, *e.g.* knee, to be influenced, and the other pole is placed on the skin near-by. When the current flows the drug passes through the skin. When it is wished to introduce potassium iodide, sodium salicylate, both used for chronic affections of joints and nerves or arsenious acid used for psoriasis, the cathode is soaked in a solution of the drug. When it is wished to introduce cocaine, used to relieve pain, copper used for ringworm and uterine discharges, or zinc used as an antiseptic or for rodent ulcer and other chronic ulcers, the anode is soaked in a solution of the drug.

Drugs are also applied to the **eye** and **ear** as drops and washes.

DOSES

The study of doses is termed **Posology.** In determining the dose the following considerations have to be borne in mind :

1. Age. The adult dose is that for a person between eighteen and sixty years old.

A common rule is, for **children** under twelve, to add twelve to the age, and divide the age by the number thus obtained. Thus for a child aged eight the dose will be $\frac{8}{8+12} = \frac{2}{5}$ of an adult dose. From twelve to sixteen years from ½ to ⅔ of the adult dose is required.

There are exceptions to these rules for individual drugs; *e.g.* children take iron, cod liver oil, arsenic, belladonna, and chloral very well, but they can take only very small doses of opium.

Above sixty years of age the dose should slightly diminish as age increases.

2. **Weight.** In pharmacological experiments the dose should always be expressed as a proportion of the weight of the animal. In man the weight is not often considered, for it depends so much upon bone and fat, which are not active tissues; but, as a rule, women require rather a smaller dose of medicine than men.

3. **Tolerance.** Towards certain drugs the body has the power of developing a remarkable degree of tolerance if they be taken repeatedly, *e.g.* daily. The result of this adaptation is that ultimately a dose many times the normal lethal amount may be taken and yet produce only the effects to be expected from the usual therapeutic quantity. Morphine is a good example of this. An addict may need 14 gr. by injection to produce the effect of ½ gr. on a normally susceptible person. For certain other drugs, *e.g.* strychnine, no tolerance is acquired. The manner in which tolerance is developed is uncertain. In some cases it may be due to quicker excretion: usually it is due to more rapid destruction in the body. If the drug be discontinued for a few weeks the tolerance is lost; a fact which is commonly observed in relation to alcohol.

4. **Intolerance or Susceptibility.** This refers to the fact that certain individuals will develop the usual symptoms of over-dosage when given a dose of certain drugs well within the normal therapeutic requirements. Susceptibility must be clearly distinguished from idiosyncrasy. As an example, $\frac{1}{200}$ gr. of atropine may produce in a susceptible person dilated pupils, dry mouth, excitability and a scarlatiniform rash, *i.e.* the usual signs of over-dosage.

5. **Idiosyncrasy** This is a peculiarity of the individual which is made apparent by his reacting to certain drugs in a wholly abnormal manner. The reaction is quite different from that normally produced by the drug in any dosage, *e.g.* agranulocytosis arising from the administration of amidopyrine or of gold salts.

6. **Time of Administration.** Drugs all act to greatest advantage when given so that their effect will be produced at its natural time. Thus soporifics act best when given in the evening, slowly acting purgatives when given overnight, quickly acting ones when given before breakfast.

7. **Mode of Administration.** We have seen that drugs are rapidly absorbed from the subcutaneous tissues. Therefore a smaller dose is required for subcutaneous injection than when the same drug is given by the mouth, for absorption is slow from the upper gastro-intestinal tract. It is usually slower

still from the rectum, but there are many individual differences with different drugs ; thus strychnine is not absorbed from the stomach, but is readily taken up from the pharynx and rectum, but prussic acid is readily absorbed from the stomach. Also certain drugs are excreted by the liver or destroyed in it when given by the stomach

8. Mental Emotion. Sometimes if the patient's mind is particularly fixed on the action of the drug a small dose is powerful. For example, often, if the patient is convinced he will sleep, a very small dose of morphine is all that may be required.

9. Temperature. Feverish patients react well to antipyretics which have but little effect on the normal temperature. Excitability may follow the use of paraldehyde if the temperature is high.

10. Preparation of Drug. A smaller dose of a liquid preparation, as a tincture, will be required than of a solid preparation of the same strength, as a pill, which will have to be slowly dissolved before absorption.

11. Rate of Excretion. It is obvious that, other things being equal, a smaller dose will be required of a drug that is slowly excreted than of one which is rapidly excreted.

12. Cumulative Action. Sometimes it is found that if a person has been taking a drug regularly, but without the production of any toxic symptoms, these will suddenly develop. This is said to be due to the cumulative action of the drug. It may be caused by the following circumstances :—

(*a*) The drug may be absorbed more rapidly than it is excreted. This is the cause of the cumulative action of mercury and lead, both of which are excreted slowly.

(*b*) There may be a sudden delay in the excretion of the drug due to disease.

(*c*) It is possible that owing to an alteration in the intestinal contents, a drug which was previously very slowly dissolved becomes quickly dissolved, and hence rapidly absorbed.

13. Disease. The physiological action of drugs, and consequently the dose, are profoundly modified by disease. For example, a patient with peritonitis will bear enormous doses of opium. Antipyretics, which do not affect a normal temperature, powerfully depress a febrile temperature.

14. Species. Different animals are often able to withstand largely different doses. Thus birds are very tolerant to opium, herbivora to atropine, and hedgehogs to many poisons, *e.g.* cantharides, and white rats are much more tolerant than brown to various toxins. This probably depends upon the different chemical compositions of the tissues of various animals.

15. Therapeutic Ratio. The *minimal lethal dose* (M.L.D.) is the amount of drug which is fatal to 50 per cent. of experimental animals. The *minimal dose* is the smallest which has therapeutic effect ; the maximal dose is the largest tolerated without toxic signs. The *therapeutic dose* lies somewhere between the two. The *therapeutic ratio* is found by dividing the therapeutic dose into the M.L.D. The higher the ratio the safer the drug.

PRESCRIBING

The more complex **prescriptions** consist of—

1. The Basis, or principal active ingredient.
2. The Ajuvans, or that which assists its action.
3. The Corrigens, or that which corrects its operation.
4. The Constituens, vehicle or excipient, which imparts an agreeable form.

For example, in Pilula Colocynthidis et Hyoscyami the colocynth is the basis, the aloes and scammony form the adjuvans, and the extract of hyoscyamus is the corrigens to prevent the griping, and soap and syrup form the vehicle. Many drugs do not require anything to assist their action or correct their operation.

Incompatibility of ingredients should be particularly avoided in prescriptions. There are three kinds of incompatibility :

(*a*) *Chemical Incompatibility.* Usually when chemical incompatibility occurs in a prescription it is due to interaction between two soluble salts leading to the formation of another salt. Sometimes chemical incompatibility is encountered designedly ; for example, perchloride of mercury is often prescribed with potassium iodide, mercuric biniodide is formed, but is kept in solution by the excess of potassium iodide. Often, however, in careless prescriptions, the interaction of soluble salts leads to the formation of a salt which is insoluble in the mixture, and a precipitate falls to the bottom of the bottle. It is important to remember that **glucosides** should not be ordered with free acids, which decompose them ; nor **alkaloids** or **alkaloidal salts** with alkalies, alkaline salts, tannic acid, iodides, or bromides, for they precipitate them. Failure to remember this has caused death, all the alkaloid being swallowed in the last dose in the bottle.

With the following drugs it is **particularly difficult to avoid chemical incompatibility** :—

Antipyrin.
Chlorine in solution.
Iodine in solution.
Liquid preparations of Iron.
Lead salts.
Zinc salts.
Silver salts.
Mercuric Chloride (especially).
All Iodides.
All Bromides.
Potassium Permanganate.
Potassium Acetate.
Nitrites.
Tannic Acid.
Gallic Acid.
Acidum Hydrocyanicum Dilutum.
Mineral Acids.
Liquor Potassii Hydroxidi.
Quinine Sulphate.
Guaiacum Tincture.

The following table, drawn up by Potter, shows the most important instances of solutions which mutually precipitate each other. P *means "forms a precipitate."*

	Alkaloidal solutions.	Metallic solutions (generally).	Lead or silver solutions.	Calcic solutions.	Magnesic solutions.	Albuminous or gelatinous solutions.
Solutions of alkalies	P	P	P	P	P	
Tannic acid	P	P	P	—	—	P
Carbonic acid and solutions of carbonates	P	P	P	P	P	
Sulphuric acid and solutions of sulphates	—	—	P	P		
Phosphoric acid and solutions of phosphates	P	P	P	P	P	
Boric acid and solutions of borates	P	P	P			
Hydrochloric acid and solutions of chlorides	—	—	P			
Hydrobromic acid and solutions of bromides	—	—	P			
Hydriodic acid and solutions of iodides	P	—	P			
Solutions of sulphides	—	P	P			
Arsenical solutions	—	P	P			
Albumen	—	P	P			

Examples of chemical incompatibility are the prescribing of (1) tannic acid or substances containing it with alkaloids or metallic salts, especially those of iron ; (2) vinegars or syrups containing acetic acid prescribed with carbonates lead to the evolution of CO_2 ; (3) strychnine sulphate is decomposed by potassium bromide, and strychnine is precipitated ; (4) chloral and alkalies form chloroform ; (5) quinine sulphate and potassium acetate together cause a voluminous precipitate of quinine acetate ; (6) lime water with mercury salts (this incompatibility is intentional in Lotio Nigra) precipitates oxides of mercury ; it decomposes carbonates and bicarbonates of alkalies ; it precipitates solutions of quinine and morphine salts ; (7) mercuric chloride is incompatible with most substances.

Substances rich in oxygen, as chlorates, iodates, permanganates, picrates, nitrates, and bichromates, should **not** be mixed **with readily oxidizable substances,** such as charcoal, sulphur, iodine, carbolic acid, glycerin, turpentine, and organic compounds generally, for explosive compounds are very liable to be formed.

Poisonous compounds may be formed by the admixture of substances in solution ; *e.g.* potassium chlorate and the syrup of iodide of iron liberate iodine : dilute hydrocyanic acid and calomel form cyanide of mercury : potassium chlorate and potassium iodide form at the temperature of the body a poisonous compound, probably potassium iodate.

If, in a mixture, incompatibility is inevitable the reacting substances should be diluted with the vehicle before being added to one another, and if a precipitate is formed it must be suspended with mucilage.

(*b*) *Physical Incompatibility.* This occurs when the mixture of the substances will not form a clear solution ; *e.g.* insoluble powders and oils will not mix with water, the addition of which to some spirits and all resinous tinctures, and to liquid extract of male fern, causes a precipitate ; an acid mixture is flavoured with liquorice, but the acid precipitates glycyrrhizin ; an alcoholic solution added to chloral causes all the chloral to rise to the top.

In the case of an insoluble powder or precipitate the liquid must be thickened so that the solid is suspended, but even then the mixture must be well shaken before a dose is measured out. Tragacanth in the form of mucilage or fine powder is usually employed to make suspensions as it keeps better than acaciæ. Pulv. Tragacanth Comp. **B.P.** (Tragacanth, Acaciæ, Starch, Sugar) is often preferred.

Oils must be made into emulsions, and for this purpose powdered acaciæ gum is most frequently chosen.

(*c*) *Pharmacological Incompatibility ; i.e.* a combination of drugs whose actions are opposed.

THE PRESCRIPTION

The details of a prescription should be written in the following order below the patient's name and address, and the date :

The *first* part is the *Superscription*, which is the sign ℞, an abbreviation for Recipe, " Take."

The *second* part is the *Inscription*, consisting of the names of the drugs in the genitive case (the vehicle in the accusative if " ad " is used with it), and their doses in the accusative.

The *third* part is the *Subscription*, that is to say, the directions to the dispenser. This in England and most other countries is sometimes written in Latin, but in France and the United States it is always in the native language.

The *fourth* part is the *Signature*, that is to say, the directions to the patient (from L. "Signetur," let it be labelled). This is written in English.

The *fifth* part consists of the doctor's name or initials at the bottom on the right.

The following are examples of prescriptions.

Superscription. ℞

Inscription. Liquoris Ferri Perchloridi ml. 1 (basis).
Quininæ Hydrochloridi G. 2 (adjuvans).
Magnesii Sulphatis G. 45 (corrigens).
Glycerin. ml. 56 (corrigens).
Infusum Quassiæ ad ml. 224 (vehicle or excipient).

Subscription. Fiat mistura.

Signature. Take one tablespoonful three times a day, two hours after meals. A. B. C. (doctor's initials).

Abbreviations. Often this prescription would be abbreviated thus : William Smith, Esq.

16th June, 1948.

Liq. Ferr. Perchlor. ml. 1.
Quin. Hydrochl. G. 2.
Mag. Sulph. G. 45.
Glycer. ml. 56.
Inf. Quass. ad ml. 224.
F. m.

Take one tablespoonful thrice a day, two hours after meals.

A. B. C.

The following is a metric prescription such as would be used on the Continent. The quantities, either of fluids or solids, are expressed in grammes, so that the abbreviation gm., or G, for this word is omitted.

William Smith, Esq. 22nd Jan., 1948.
Address....................

℞	Magnesiæ Sulphatis	30
	Acidi Sulphurici Diluti	0·6
	Syrupi Limonis	30
	Aquæ	180

Fiat haustus.

To be taken on rising in the morning.

A. B. C.

The following is a **D.D.A.** prescription :

180 Wimpole Street,
W.1.

W. Smith, Esq.
112 Acacia Road,
London, W.1.

24th Jan., 1948.

℞. Diamorphin. hydrochlor. . gr. $\frac{1}{16}$
Syr. Tolu. . . . . ♏ xxx.
Aq. ad. . . . . ʒ ii.

Fiat mist. Mitte ℥ vi.
Sig. Two teaspoonfuls to be taken four-hourly.

Total drug : 1½ grains.
Not to be repeated.
J. Atkinson,
M.D.

Abbreviations should be employed as little as possible. The "British Pharmacopœia" published 1914 was the first giving an abbreviation for each official substance and preparation. Serious mistakes have happened because the abbreviations have been ambiguous. The following are especially to be avoided :

Acid. Hydroc. (may be either Acidum Hydrochloricum or Acidum Hydrocyanicum).

Hyd. Chlor. (may be either Calomel, Corrosive sublimate, or Chloral hydrate).
Hyd. ,, ,, Hydrargyrum, Hydras, Hydriodas, Hydrochloras, Hydrochloridum, or Hydrocyanicus).
Sulph. (,, ,, Sulphur, Sulphide, Sulphate, or Sulphite).

Sometimes the signature is written in Latin, and it is often abbreviated. A list of abbreviations is in the Appendix.

In Great Britain it is understood, unless otherwise stated, that preparations are those of the British Pharmacopœia.

Ad. Be careful in deciding whether or not to use this word before the vehicle, as the proportion of ingredients to the whole is altered by it.

Dispensing the Prescription. The dispenser should bear the following rules in mind :—(1) Read the prescription through first. (2) Next write the directions, so that they have time to dry. (3) Solution by heat should not be used if more of the salt is ordered than will dissolve in cold water. In such a case it must be suspended. (4) With fluids, measure them in such an order that the measure-glass shall be finally rinsed out with the vehicle. (5) Use glass scale pans. (6) Clean and put away everything directly after use. (7) If in the slightest doubt ask the prescriber. (8) If finally the prescription contains any insoluble matter, label "Shake the bottle." (9) If the medicine is very poisonous, and for outward application only, label it as such and use a distinctive bottle. (10) In dispensing substances chemically incompatible, if there is any likelihood that the new body formed is dangerous, communicate with the prescriber before dispensing (*e.g.* alkaloids are precipitated by alkalies). Otherwise keep the incompatibles as far apart as possible by diluting each with the vehicle before mixing.

Dangerous Drugs Acts (1920 & 1925). The following regulations apply to Morphine, Pethidine, Synthetic Cocaine, Cocaine, Ecgonine, their respective salts, medicinal Opium, and any preparation or admixture containing not less than 0·2 per cent. of anhydrous morphine or 0·1 per cent. of cocaine, synthetic cocaine, or ecgonine. They also apply to any extract or tincture of Indian hemp, dicodide and its salts, pethidine and its salts, and any preparation containing any proportion of diamorphine, dihydro-oxycodeinone, dilaudide and acedicone. They state that prescriptions containing a larger proportion of these drugs must comply with the following conditions: (1) Prescriptions must be in writing. (2) Must be signed with full name and address of prescriber and dated and bear the words "Not to be repeated," or "To be repeated once (or twice) at ...... day intervals." (3) Must specify the name and address of the person for whom intended. (4) Must specify the total amount of the drug to be supplied and the dose to be taken. If the preparation ordered is in the B.P., B.P.C., or Drug Tariff issued by the Ministry of Health, it will suffice if the total amount of the preparation to be supplied is given. A dentist should write on his prescription "for local dental treatment only."

Poisons Rules (1935). After May 1st, 1936, a large number of drugs became subject to restrictions very similar to those of the **D.D.A.** The regulations for prescription writing are in fact the same, except that under the **D.D.A.** instructions may be given to repeat the dispensing on two occasions only at stated intervals; the **Poisons Rules** permit several repetitions provided that the intervals are defined in the prescription. The total amount of the finished product of dispensing must be stated. Note also that a practitioner is responsible for keeping a register of drugs purchased for use in his practice if they are included in the **D.D.A.** This does not apply to the drugs affected by the new **Poisons Rules** unless they fall also under the **D.D.A.** The **First Schedule of Poisons** includes a large number of drugs in addition to those listed under the **D.D.A.** Of these, special mention should be made of codeine, digitalis glucosides and ouabain. For the doctor the memorizing of the entire list is unnecessary. In general it is safe to assume that whenever a poisonous, as opposed to a comparatively non-toxic, drug is prescribed it is as well to assume that it is included in the Schedule.

The rules affect substances in the **Fourth Schedule of Poisons**. The following are the most important members of this group :—Amidopyrine, Amytal, Barbituric acid and its derivatives, Cinchophen (atophan), Dekrysil, Methylsulphonal, Novatophan, Salicylcinchoninic acid, Sulphonal, Sulphonamides, Theominal, Trional.

The regulations, although adding greatly to the labour of the prescriber and dispensing chemist, are nevertheless to be welcomed in that they deal an effective blow at many proprietary preparations which contain drugs of considerable toxicity. Amidopyrine (pyramidon) and Cinchophen (atophan) are examples of this. The former may produce agranulocytosis; the latter fatal toxic hepatitis.

PHARMACOLOGICAL AND THERAPEUTIC ACTIONS

When the action of a drug is spoken of, the physiological action is usually understood.

The primary action is that due to the unaltered drug; *e.g.* the emetic action of sulphate of zinc.

The secondary action is that due to compounds formed from the drug whilst in the body; *e.g.* the antiseptic effect on the urine of hexamine taken by the mouth is due to the liberation of formaldehyde in acid urine.

The direct or local action of a drug is that produced on any organ with which it comes in contact; *e.g.* the cantharidin in cantharides, in being excreted through the kidneys causes inflammation of them.

The indirect or remote action is a secondary effect, the result of the direct effect; *e.g.* curare paralyses the respiratory muscles, consequently the blood becomes venous, and therefore convulsions take place. The venosity and the convulsions are each indirect actions of curare.

Relation between Chemical Constitution and Physiological Action. There is no doubt that the physiological action of a drug often depends upon its chemical constitution. Naturally, substances which are broken up in the body in such a way as to lead to the liberation of a common element or group will have a similar action. The action of a drug also depends upon electrolytic dissociation of its solutions, and then the effect depends upon which ion is the more poisonous. For example, the hydrochloride and sulphate of strychnine will have the same action owing to the intensity of action of the strychnine ion, and because the chlorine and sulphate ions can be disregarded, for the animal would be killed by the strychnine ion before enough of the chloride or sulphate ions could be given to have any influence. But with sodium chloride and sodium sulphate the action is quite different, because, the sodium being almost harmless, sufficient quantity of the drugs can be given for the chlorine and sulphate ions to have their separate effects.

Instances in which chemical constitution obviously influences action are the similarity of effects of nitrites, the fact that all chlorides, bromides, and iodides of ethane and methane are anæsthetic, the similarity of action of iodides of many metals and the similarity of action of bromides of many metals.

Substitution of one radical for another in organic compounds often strikingly modifies their action ; for example, if strychnine, brucine, and thebaine are converted into methylstrychnine, methylbrucine, and methylthebaine, the convulsive action of each of the first three substances is replaced by a paralysing action. The effect of substitution may be also well seen in the various derivatives of atropine and cocaine, and in the relation of aconitine (*q.v.*) to benzaconine and aconine. Another very interesting case in point is that methyl glucoside is sweet, ethyl glucoside is somewhat sweet, phenyl glucoside is bitter, and benzyl glucoside is intensely bitter.

Sometimes the position of the radicals in the molecule is of great physiological importance : thus resorcin (metadihydroxybenzene) is very sweet, whilst pyrocatechin (orthodihydroxybenzene) is bitter.

Sometimes the molecular weight appears to influence the intensity of action, for the relative toxicity of various alcohols is as follows : methyl alcohol, 0·8 ; ethyl alcohol, 1·0 ; propyl alcohol, 2·0 ; butyl alcohol, 3·0 ; amyl alcohol, 4·0.

Relation between Physical Condition and Physiological Action. The physical condition must obviously influence the action. For example, a volatile drug can act directly on the respiratory mucous membrane, and it can be absorbed very rapidly. Drugs insoluble in the gastro-intestinal fluids act very slowly unless given in solution. Again, the rate and direction of diffusion must depend upon whether the solution of the drug is isotonic, hypotonic, or hypertonic as regards the fluid, usually within cells, with which its solution is diffusing. Inasmuch as the results of diffusion are best seen with solutions of salts of alkaline metals, effects on the body which result from diffusion are said to be due to "*salt action.*"

Colloidal Solutions or Collosols. These solutions are suspensions of minute particles of a substance in the colloidal state (*i.e.* they are amorphous and diffuse with difficulty). Many substances, chiefly metals, can, it is now known, exist in both colloidal and crystalloid states. In order to remain in the colloidal state metals require in the solution some organic colloid, *e.g.* albumin. Collosols can be made either chemically or electrically. When the solvent is water the colloidal solution is sometimes called a hydrosol. Collosols of iodine, silver and sulphur have been used externally for skin diseases. Injected subcutaneously they produce a leucocytosis. Large doses can be given by the mouth, for substances in the colloidal form can only be absorbed slowly. Collosols of silver and mercury, and to a less extent of other metals, have been given internally. There is no evidence that the therapeutic effect of drugs in the colloidal state is better than that of the same drugs in the crystalloid state.

MATERIA MEDICA

PART I

Substances used chiefly for their Local Action

GROUP I

Demulcents, Emollients, Oleates and Dusting Powders

Demulcents. Mucilaginous or emulsified substances used for the protection of mucous surfaces.

USES. 1. To cover inflamed and irritated surfaces, *e.g.* sore throat (lozenges), and irritant poisoning.

2. As basis for enemata intended to be retained.

3. For suspension of insoluble drugs.

4. For raising viscosity of blood ; here administered intravenously, *e.g.* 6 per cent. gum acacia in shock.

5. For masking flavours or rendering fluids more bland, *e.g.* barley water.

Liquorice is used chiefly to mask unpleasant tastes, especially that of ammonium chloride. It is only slightly laxative and it is the senna and sulphur of the compound powder which are responsible for its action.

TRAGACANTH

Tragacantha (B P.). A gummy exudation from *Astragalus gummifer*.

COMPOSITION. The chief constituents are—1. *Tragacanthin*, a gum, 33 per cent., only slightly soluble in water, unfermentable. 2 An *Arabin*-like gum, 53 per cent., soluble in water, precipitated by lead acetate or ferric chloride.

Preparations **(B.P.)**

1. **Mucilago Tragacanthæ.** Tragacanth, 1·25 ; alcohol, 2·5 ; water, 100.

Dose, 60—240 min. 4—16 ml.

2. **Pulvis Tragacanthæ Compositus.** Tragacanth, 15 gum acacia, 20 ; starch ; sugar.

Dose, 10—60 gr. 0·6—4 G.

ACACIA

Acacia (B.P.). *Synonym.* Gum Acacia. A gummy exudation from the stem and branches of *Acacia senegal.* It is one of the varieties of Gum Arabic.

Solubility. Freely in water, not in alcohol.

Composition. The chief constituent is *arabin,* or *arabic acid,* $C_6H_{10}O_5$.

Preparation **(B.P.)**

Mucilago Acaciæ. Acacia, 2; chloroform water, 3. Should be recently prepared.

Dose, 60—240 min. 4—16 ml.

LIQUORICE

Glycyrrhiza (B.P.) *Synonym.* Liquorice Root. The peeled or unpeeled root and subterranean stems of *Glycyrrhiza glabra.*

Composition. The chief constituents are—1. *Glycyrrhizin,* a yellow amorphous glucoside, $C_{24}H_{36}O_9$. 2. Asparagin. 3. Grape sugar, resin, starch, gum, and malic acid.

Dose, 15—60 gr. 1—4 G.

Preparations **(B.P.)**

1. **Extractum Glycyrrhizæ.** Liquorice root percolated with chloroform water.

Dose, 10—30 gr. 0·6—2 G.

2. **Extractum Glycyrrhizæ Liquidum.** Liquorice root; chloroform water; alcohol (90 per cent.), q.s.

Dose, 30—60 min. 2—4 ml.

3. **Pulvis Glycyrrhizæ Compositus.** Senna, 16; liquorice root, 16; fennel, 8; sublimed sulphur, 8; sugar.

Dose, 60—120 gr. 4—8 G.

LINSEED

Linum (B.P.C.). The dried ripe seeds of *Linum usitatissimum.*

Oleum Lini (B.P.). Linseed Oil.

Source. Expressed from linseed.

Characters. It is viscid, yellow fixed oil, commonly called "drying oil" because it unites with oxygen and becomes resinoid on exposure.

Dose, ½—1 fl. oz. 15—30 ml.

STARCH

Amylum (**B.P.**). $(C_6H_{10}O_5)n$. The starch procured from maize, rice, wheat, or potato.

Preparation (**B.P.**).

Glycerinum Amyli. Starch, 85 ; glycerin, 745 ; water.

Emollients. Greasy or oily substances used for protection and softening of the skin. They also aid the penetration of drugs which have been dissolved in them.

LARD

Adeps (**B.P.**). Lard. The purified internal fat of the hog, *Sus scrofa.*

COMPOSITION. 1. Olein, 60 per cent. 2. Stearin 3. Palmitin.

Lard is contained in many ointments.

In India, Suet should be employed in making the official preparations for which Lard is directed to be used.

Preparation (**B.P.**)

Adeps Benzoinatus. Prepared lard, 1000 ; Benzoin in coarse powder, 20.

WOOL-FAT

Adeps Lanæ (**B.P.**). Wool-fat. *Synonym.* Anhydrous Lanolin. The purified fat of sheep's wool freed from water.

CHARACTERS. Semi-transparent, yellow, tenacious. Melts about 40° C. *Solubility.* Freely in chloroform and in ether, partially in alcohol.

Adeps Lanæ Hydrosus (**B.P.**). Hydrous wool-fat. *Synonym.* Lanolin.

SOURCE. Incorporate 3 of water with 7 of wool-fat by melting and mixing in a warm mortar.

CHARACTERS. Opaque, very pale yellow, softer than wool-fat.

Alcoholia Lanæ (**B.P.**). Wool alcohols are prepared by saponification of the grease of sheep's wool, and the separation of the fraction containing cholesterol and other alcohols.

CHARACTERS. A golden solid becoming plastic when warm. Contains 28 per cent. of cholesterol. *Solubility.* Free in ether and chloroform.

Preparation (**B.P.**)

Unguentum Alcoholium Lanæ. Wool alcohols, hard, soft, and liquid paraffin.

Action and Therapeutics

The above emollients are used as the basis of ointments.

LIQUID PARAFFIN

Paraffinum Liquidum (B.P.). Liquid paraffin is a mixture of liquid hydrocarbons.

Characters. A transparent colourless, odourless, tasteless, clear oily liquid. Sp. gr. 0·880 to 0·895.

Dose, ¼—1 fl. oz. 7·5—30 ml

Preparation (**B.P.**)

Emulsio Paraffini Liquidi. Liquid paraffin, acacia, tragacanth, glycerin, sodium benzoate, vanillin, chloroform, and water.

Dose, ¼—1 fl. oz. 8—30 ml.

LIGHT LIQUID PARAFFIN

Paraffinum Liquidum Leve (B.P.). *Unoff. Synonyms.* Spray Paraffin, Paroleine.

Characters. Light liquid paraffin is similar to liquid paraffin, but the sp. gr. is 0·835 to 0·875.

HARD PARAFFIN

Paraffinum Durum (B.P.). Hard paraffin is a mixture of solid hydrocarbons.

Characters. A somewhat translucent, colourless, crystalline, inodorous, tasteless solid, slightly greasy to the touch. Melts at 50° to 60° C. *Solubility.* Freely in ether and chloroform; slightly in alcohol.

WHITE SOFT PARAFFIN

Paraffinum Molle Album (B.P.). White soft paraffin is a bleached mixture of semi-solid hydrocarbons.

Characters. A white or yellowish, translucent, soft and greasy semi-solid, free from any unpleasant odour or flavour. Melts at 42° to 46° C.

YELLOW SOFT PARAFFIN

Paraffinum Molle Flavum (B.P.). A mixture of hydrocarbons obtained from petroleum.

Characters. Similar to the white variety.

Preparation (B.P.)

Unguentum Paraffini. Hard Paraffin, soft paraffin, white beeswax. When paraffin ointment is the basis of white ointments, it should be made from white soft paraffin; when it is the basis of coloured ointments it should be made from yellow soft paraffin. In order to meet the exigencies of climate and temperature the proportion of hard and soft paraffin may be varied.

Therapeutics

Paraffins do not become rancid, or irritate the skin, and thus form a good basis for ointments. Hard paraffin has recently been used for the treatment of sprains and chronic inflammatory conditions of the joints. It is melted, and applied in several layers at a temperature of 60–65° C. The light liquid paraffin is suitable for the preparation of nebulæ and sprays.

Liquid paraffin is unabsorbed from the alimentary canal, but is an excellent aperient for many persons, producing if taken over-night an easy motion of the bowels without any griping. With some it has little action, and in others it may pass through the bowels and out of the anus without bringing any motion with it. This can be avoided by taking small doses (2 drs.) after meals rather than one large dose at night. Seepage is less likely to occur with the emulsion. It is also more pleasant to take.

WAX

Cera Flava (B.P.). Yellow Beeswax. Prepared from the honeycomb of the hive bee, *Apis mellifica.*

Characters. Firm yellowish. Odour honey-like. Soluble in oil of turpentine, not in alcohol. It is much adulterated with other waxes, resin and paraffin.

Composition. It consists chiefly of 1. Myricin (Myricyl palmitate) $C_{30}H_{61}C_{16}H_{31}O_2$, 80 per cent. 2. Cerotic acid.

Cera Alba (B.P.). White Beeswax. Made by bleaching yellow beeswax.

Cera Emulsificans (B.P.). Consists of cetostearyl alcohol, sodium lauryl sulphate and water.

It is an ingredient of penicillin creams.

Preparations **(B.P.)**

1. **Unguentum Emulsificans.** Emulsifying wax, soft and liquid paraffin.
2. **Unguentum Emulsificans Aquosum.** Emulsifying ointment, chlorocresol and water.

HYDROUS OINTMENT

Unguentum Aquosum (B.P.). Ointment of wool alcohols; distilled water, equal parts.

SIMPLE OINTMENT

Unguentum Simplex (B.P.). Wool-fat; hard and soft paraffin.

Therapeutics

Yellow and white wax are only used as bases for many plasters and ointments. Hydrous and simple ointments are used as bases for certain ointments and as simple emollients. Emulsifying wax is used in creams.

OLIVE OIL

Oleum Olivæ (B.P.). The oil expressed from the ripe fruit of *Olea europæa*, and refined.

CHARACTERS. A pale yellow or greenish yellow fluid. Odour faint. Sp. gr. 0·915 to 0·918.

COMPOSITION. The two constituents are—1. *Olein*, 72 per cent., a fluid oil. 2. *Palmitin*, nearly 28 per cent., a solid oil.

Olive oil is contained in many plasters, ointments, and liniments. From it are made hard soap, soft soap, and glycerin.

Dose, ½—1 fl. oz. 15—30 ml.

Action and Therapeutics

External. Olive oil is employed in massage, especially when the skin is unusually dry, in ichthyosis, and when the integument is being subjected to increasing tension, *e.g.* breast and abdominal swelling in pregnancy. It appears to penetrate the skin and to reduce the tendency under this condition to the formation of striæ atrophicæ. It is still unfortunately used as a protective to burns, but facilitates microbial growth.

Internal. For its soothing protective qualities it may be swallowed after corrosive poisons have been taken. All fats retard gastric and accelerate pancreatic secretion. Because olive oil retards the flow of the gastric juice and delays emptying of the stomach it is excellent in cases of gastric and duodenal ulcer. Its value as a food is considerable. It is a mild laxative, and can be given with other food for this purpose. It often, however, excites nausea and vomiting. In the duodenum it is split up into glycerin and fatty acids which form soaps. An olive oil enema (warm olive oil, 5 fl. oz.—150 ml.; with or without warm mucilage of starch, 8 fl. oz.—240 ml.) is used to open the bowels when a mild non-irritating injection is required.

Some patients suffering from cholecystitis derive much benefit from taking olive oil. Possibly this is because the oil stimulates outpouring of bile and thus drains the infected viscus. From 2 to 8 fl. oz. (60 to 240 ml.) should be taken daily.

OLEIC ACID

Acidum Oleicum (B.P.).

CHARACTERS. A straw-coloured oily liquid, nearly odourless and tasteless. It becomes semi-solid at 40° F. *Solubility.* Easily in alcohol, chloroform, and ether.

Lead plaster contains oleate of lead, and *Zinc oleate ointment contains* oleate of zinc. Hydrargyrum Oleatum is also official.

Dose, 5—15 min. 0·3—1 ml.

Action and Therapeutics

Oleic acid is used as a solvent for remedies which it is desired to apply by means of cutaneous inunction, for it more readily penetrates the skin than fats and oils. It is particularly useful as it will dissolve most metallic oxides and all alkaloids (but not their salts), forming oleates dissolved in the excess of oleic acid. Hence its employment in the official preparations mentioned above.

Æthanolamine

Æthanolamina (B.P.). A clear colourless fluid prepared by the action of ammonia on ethylene oxide.

Preparation (B.P.)

Injectio Æthanolaminæ Oleatis. Æthanolamine, 0·9; oleic acid, 4·2; benzyl alcohol; water to 100.

Dose, 30—75 min. 2—5 ml. by intravenous injection.

Therapeutics

A sclerosing fluid for the treatment of varicose veins.

ARACHIS OIL

Oleum Arachis (B.P.). *Synonyms.* Ground-nut oil, pea-nut oil. The oil expressed from the seeds of *Arachis hypogœa.*

Characters. Pale yellow or greenish-yellow ; nut-like odour.

Dose, ½—1 fl. oz. 15—30 ml.

SESAME OIL

Oleum Sesami (B.P.). The oil expressed from the seeds of *Sesamum indicum.*

Characters. A limpid oil of a pale yellow colour, a faint odour, and a bland taste.

Dose, ½—1 fl. oz. 15—30 ml.

Therapeutics

Arachis and sesame oils are now authorized to replace olive oil in certain official preparations.

COTTONSEED OIL

Oleum Gossypii Seminis (B.P.). A fixed oil obtained from the seeds of *Gossypium.*

Characters. Pale yellow odourless oil. Bland taste.

Dose, ½—1 fl. oz. 15—30 ml.

Uses

It is used chiefly externally as an emollient or internally as a demulcent in the place of olive oil. It has the advantage of being cheaper.

ALMONDS

Amygdala Dulcis (B.P.C.). Sweet Almond. *Unoff. Syn.* Jordan almond. The ripe seed of *Prunus communis.*

Composition. The chief constituents are—1. *Oleum Amygdalæ,* 50 per cent., the same fixed oil as in bitter almonds. 2. Emulsin and other albuminous bodies.

Amygdala Amara (B.P.C.). Bitter Almond. The ripe seed of *Prunus communis.*

Characters. Like the sweet almond, but with a bitter taste.

Oleum Amygdalæ Volatile Purificatum (B.P.). The essential oil of bitter almonds freed from prussic acid, which may be present up to 10 per cent. in the untreated oil.

Dose, ¼—1 min. 0·016—0·06 ml.

Oleum Amygdalæ (B.P.).

Source. The fixed oil obtained by expression from either sweet or bitter almonds.

Characters. Pale yellow, nearly inodorous, with an oleaginous, nutty taste. *Solubility.* Slightly in alcohol, easily in ether or chloroform.

Dose, ½—1 fl. oz. 15—30 ml.

Action and Therapeutics

The sweet almond is demulcent. Its most important medicinal use is that it is made into flour to replace starchy food in cases of diabetes.

The almond mixture is a very pleasant vehicle for the suspension of insoluble substances, *e.g. terebene in cough medicines.* The powder is a palatable basis for powders and a useful demulcent in the *preparation of cough mixtures.*

Oleum Amygdalæ might be used for the same purposes as olive oil. It is pleasanter, but expensive.

GLYCERIN

Glycerinum (B.P.). $C_3H_5(OH)_3$.

Source. It is obtained by hydrolysis by the interaction of alkalies or of superheated steam with fats and fixed oils.

Characters. Clear, colourless, odourless with sweet taste. It is miscible with water and alcohol.

Dose, 60—120 min. 4—8 ml.
30—120 min. 2—8 ml. by rectal injection.

Preparations

1. **Glycerinum Acidi Borici (B.P.).** Powdered boric acid; glycerin. It is a 30 per cent. solution of Glyceryl Borate in Glycerin.
Dose, 10—30 min. 0·6—2 ml.

2. **Glycerinum Acidi Carbolici.** Carbolic acid in glycerin. Strength, 20 per cent.

3. **Glycerinum Acidi Tannici (B.P.).** Tannic acid, 15; glycerin, 85.
Dose, 10—30 min. 0·6—2 ml.

4. **Glycerinum Amyli (B.P.).** Starch, 85; glycerin, 745; water, 17.

5. **Glycerinum Boracis (B.P.).** Borax in glycerin. Strength, 12 per cent.
Dose, 30—60 min. 2—4 ml.

6. **Glycerinum Pepsini (B.P.C.).** Pepsin, 100; hydrochloric acid, 11·5; glycerin, 600; distilled water to 1000. *Strength*, 1 fl. dr. contains about 5·5 gr. of pepsin; 10 ml. contain 1 G.
Dose, 60—120 min. 4—8 ml.

7. **Glycerinum Phenolis (B.P.).** Glycerin of Phenol. Phenol in glycerin. *Strength*, 16 per cent.
Dose, 5—15 min. 0·3—1 ml.

8. Suppositorium Glycerini (B.P.). Gelatin, 14; glycerin, 70; water, to make 100; each suppository contains 70 per cent. of glycerin. They must be kept wrapped in waxed paper, as they absorb moisture.

Action

External. As glycerin is an excellent solvent for numerous bodies, such as iodine, bromine, alkalies, tannic acid, many neutral salts, alkaloids, and salicin, it is a good vehicle for applying these substances to the skin and to sores. It does not evaporate nor turn rancid, and is powerfully hygroscopic.

Internal. In man the only visible effect produced by its administration is **purging.** This occurs with quite small doses if it is given by the rectum, but large doses are necessary if given by the mouth. It is absorbed from the alimentary canal, and is to a slight extent a food, for some of it is oxidized in the body.

Therapeutics

External. Glycerin is much employed as a basis for applications to the skin and the eye. It is commonly used for chapped hands and slight excoriations. Its hygroscopic properties are made use of in the employment of such substances as cataplasma kaolin, of pastes made with magnesium sulphate to hasten discharge from boils, and of vaginal suppositories.

Internal. As glycerin is sweet it is an excellent flavouring agent. It is demulcent, and is used as a vehicle for applying substances, such as tannic acid, to the throat. Glycerin is rarely given by the mouth for any medicinal virtue. One to two fluid drachms injected up the rectum, or a glycerin suppository, form an excellent means of opening the bowels in simple constipation and dyschezia. No pain or constitutional disturbance is produced.

GELATIN

Gelatinum (B.P.). The air-dried product of the action of boiling water on skin, tendons, ligaments, and bones.

Characters. The solution in hot water is colourless and inodorous; it solidifies to a jelly on cooling. It is insoluble in alcohol or ether. Its aqueous solution is precipitated by tannin.

Uses

It is a useful basis for suppositories, pessaries, bougies, discs, gelatin capsules and lozenges, and as a coating for pills.

Dusting Powders. These are mechanical agents which act by protecting the skin against irritation by clothes and have the particular advantage of keeping the surface dry. They are of special value, therefore, for application to the flexures. Those commonly used are **Talc** (magnesium silicate), **Kaolin** (see **Alum**), **Fullers' Earth** (aluminium silicate) and **Lycopodium.** The last-named is efficacious because it does not become sodden in water and is thus of value for dusting the skin about the genitalia in cases of incontinence of urine.

GROUP II

Carbohydrate Nutrients and Flavouring Agents

SUGAR

Sucrosum (B.P.). $C_{12}H_{22}O_{11}$. *Synonyms.* Refined Sugar. Saccharum Purificatum.

Preparations (B.P.)

1. **Syrupus.** Refined sugar dissolved in water. Sp. gr. 1·330.
2. **Syrupus Glucosi Liquidi.** Syrup, 2 glucose, 1.

Action and Therapeutics

Sugar and syrup are sweetening agents and foods. Syrupus Glucosi is used in pharmacy, especially in the making of pills, as it forms a neutral basis.

LACTOSE

Lactosum (B.P.). $C_{12}H_{22}O_{11}$, H_2O. *Synonym.* Milk Sugar Saccharum Lactis.

Characters. White crystalline masses or white powder. Slightly sweet. *Solubility*, 1 in 7.

Therapeutics

As it is not hygroscopic, it is used to give bulk to powders. It has been advocated for administration in drachm doses in order to alter the intestinal flora when an excess of non-lactose-fermenting organisms is present. It is used in humanizing cows' milk. Taken in the morning ($\frac{1}{2}$ oz.) in tea, it acts as a mild laxative, especially valuable for those suffering from intestinal flatulence.

DEXTROSE and GLUCOSE

Dextrosum (**B.P.**). $C_6H_{12}O_6$. Prepared from starch by hydrolysis.

Preparation (**B.P.**)

Injectio Dextrosi. Contains 5 per cent. w/v.

Dextrosum Hydratum (**B.P.**). $C_6H_{12}O_6$, H_2O. *Synonym.* Medicinal glucose.

Glucosum Liquidum (**B.P.**). Glucose is a mixture of dextrose (**Dextrosum** : **B.P.**) $C_6H_{12}O_6$, maltose, dextrin and water, and is obtained by the hydrolysis of starch.

Characters. A very viscous syrup, almost colourless. No odour. Taste sweet. Freely soluble in water.

Preparation (**B.P.**)

Syrupus Glucosi Liquidi. Glucose, 1 ; syrup, 2.

Action and Therapeutics

Glucose is a most valuable food for debilitated or feverish patients, for it requires no digestion prior to assimilation. It is thus of great value in typhoid fever. The official dextrose is pure $C_6H_{12}O_6$ and most suitable for this purpose. The Liquor Dextrosi et Sodii Chloride (**B.P.C.**) containing 5 per cent. w/v of dextrose in 0·9 per cent. of sodium chloride, though slightly hypertonic, is valuable for intravenous administration. Up to 10 per cent. can usually be tolerated and absorbed per rectum. Sugar is better absorbed from the rectum than any other food. Glucose (5 per cent.), by mouth or intravenously, is the best treatment for acidosis. By raising the glycogen content of the liver, it appears to increase the resistance of this organ to various poisons, *e.g.* chloroform and novarsenobenzol, and should be given prior to their administration. It promptly relieves symptoms of spontaneous hypoglycæmia and that due to insulin over-dosage, and is given in conjunction with this substance in the treatment of diabetic coma. Good results may follow its use in asthma, cyclical vomiting of children, and migraine.

Hypertonic solutions (25 per cent.) are given intravenously in order to reduce intracranial pressure and to restrict loss of fluid from the bowel in cholera. The action depends upon the high osmotic pressure of the solution.

Solutions of dextrose (50 per cent.) have been used for injecting varicose veins. The clot formed is not firmly attached to the vein wall, however, and fatal embolism may arise.

LÆVULOSE

Lævulosum (B.P.) $C_6H_{12}O_6$. *Synonym.* Fructose. Obtained from invert sugar or honey.

CHARACTERS. White, hygroscopic, crystalline powder of sweet taste. Freely soluble.

Therapeutics

Lævulose is used chiefly as a means of testing hepatic efficiency. Fifty grams are given in solution and the blood sugar estimated every half-hour afterwards for two hours. The rise should be very slight, the maximum normal being 25 mgms. above fasting level, which should be regained in one and a half hours at the latest. If 30 mgms. or more, it indicates gross liver damage.

MALT

Malt or byne is the seed of common barley, caused to enter the incipient stage of germination by heat and then dried. It contains the ferment diastase, which can convert starch into dextrin and finally to maltose. Thus $(C_6H_{10}O_5)_2n$ starch + $nH_2O = nC_{12}H_{22}O_{11}$ maltose.

EXTRACT OF MALT

Extractum Malti (B.P.).

SOURCE. It is prepared in many ways from malt, but the basis of them all is that malt is macerated with water and evaporated to the consistency of a thick extract.

Composition. It contains *maltose*, $C_{12}H_{22}O_{11}$; dextrin $(C_6H_{10}O_5)n$, and diastase.

Characters. A sweet, thick, brownish liquid, like honey. It forms an emulsion with oils. Miscible with water.

Dose, 60 min.—1 fl. oz. **4—30 ml.** daily, in divided doses.

Action and Therapeutics

Malt extract is a food because of its carbohydrate content and the presence of vitamin B, especially B_1. It is easily tolerated. The small amount of diastase present is of little importance in assisting the digestion of farinaceous food. Emulsions of cod-liver oil in malt extract are useful, and of pleasant taste.

HONEY

Mel Depuratum (B.P.). Melt honey in a water-bath, and strain while hot.

Characters. A thick, yellowish liquid, sp. gr. 1·36, translucent when fresh, but becoming opaque and crystalline. Lævorotatory and faintly acid.

Composition. About 70 per cent. of dextrose and lævulose; also wax, dextrin, volatile oil and pollen.

Preparation (B.P.)

Oxymel. Purified honey, 700; acetic acid, 150; water, 150. Sp. gr. 1·26.

Dose, 30—120 min. **3—8 ml.**

Purified honey is contained in Oxymel Scillæ and Mel Boracis.

Action and Therapeutics

Honey is demulcent, relieving dryness of the mouth and facilitating swallowing. Oxymel is a useful preparation. It is a common ingredient of cough mixtures. Honey is a mild laxative, and may be given to children for this purpose.

SACCHARIN

Saccharinum (B.P.). $C_7H_5O_3NS$. *Unoff. Synonym.* Gluside.

Characters. A white crystalline powder. Its solution has an intensely sweet taste; 1 of saccharin is equal to 300 of cane sugar. *Solubility.* 1 in 400 of cold water; 1 in 24 of boiling water; 1 in 500 of chloroform; 1 in 25 of alcohol (90 per cent.); 1 in 48 of glycerin. It unites with alkaline hydrates

OD TECHNOLOGICAL RESEARCH

and carbonates, evolving from the latter carbonic acid gas, and yielding soluble saccharin, which has lost none of its sweetness, and is very soluble in water.

SOLUBLE SACCHARIN

Saccharinum Sodium (B.P.), $CO . C_6H_4 . SO_2NNa, 2H_2O$

Source. The sodium derivative of saccharin from which it is derived by the action of sodium hydroxide.

Characters. White, crystalline powder; intensely sweet. *Solubility.* 1 in 1·5 of water.

Action and Therapeutics

It is employed as a **sweetening agent** when from any cause, as diabetes or obesity, sugar cannot be taken.

GROUP III

Bitters

Calumba, Gentian, Quassia, Orange Peel.

The group of " bitters " comprises substances quite unrelated chemically, but all possessing the common property of an intensely bitter taste. These drugs are given to promote appetite and thus to aid digestion. The action is entirely on the gustatory nerves and results in increased flow of saliva and gastric juice. If introduced directly into the stomach they have no such effect. The simple bitters have no general action, but powerful drugs such as quinine or strychnine may be used in small doses only for their bitter taste.

Some bitters are also astringents on account of their tannic acid content, *e.g.* gentian, and must not be prescribed with metals; the majority are known as simple bitters, *e.g.* calumba and quassia; a third group is comprised of aromatic bitters, these substances containing volatile oils in addition to the bitter principle, *e.g.* orange peel, and may be used as flavouring agents. Calumba, gentian and quassia are those in common use.

It is of interest to note that the pharmacological action of bitters on gastric secretion is noticeable in cachectic dogs, but not in healthy animals. It is for conditions associated with debility and anorexia that they have proved useful in clinical work.

CALUMBA

Calumba (B.P.). Calumba Root.

Musty odour, bitter taste.

No tannin is present, so calumba can be prescribed with salts of iron.

Dose, 10—30 gr. 0·6—2 G.

Preparations **(B.P.)**

1. **Infusum Calumbæ Recens.** Calumba root; cold water (to avoid extracting the starch).

   Dose, ½—1 fl. oz. 15—30 ml.

2. **Infusum Calumbæ Concentratum.** Calumba root, alcohol (90 per cent.), water q.s.

   Dose, 30—60 min. 2—4 ml.

3. **Infusum Calumbæ.**

   Dose, ½—1 fl. oz. 15—30 ml.

4. **Tinctura Calumbæ.** Calumba root; alcohol (60 per cent.). Macerate.

   Dose, 30—60 min. 2—4 ml.

GENTIAN

Gentiana (B.P.) The dried rhizome and root of *Gentiana lutea.*

Composition. The bitter constituents are glucosides. Gentian contains a trace of tannin only, but cannot be prescribed with iron, because that darkens the colouring matter.

Dose, 10—30 gr. 0·6—2 G.

Preparations **(B.P.)**

1. **Infusum Gentianæ Compositum Concentratum;** Gentian, 1; dried bitter orange peel, 1; lemon peel, 1; alcohol (25 per cent.), 12.

   Dose, 30—60 min. 2—4 ml.

2. **Infusum Gentianæ Compositum.**

   Dose, ½—1 fl. oz. 15—30 ml.

3. **Tinctura Gentianæ Composita.** Gentian, 100; dried bitter orange peel, 37·5; cardamoms; alcohol (45 per cent.), 1000. Macerate.

   Dose, 30—60 min. 2—4 ml.

QUASSIA

Quassia (B.P.). The wood of the trunk and branches of *Picræna excelsa.*

No tannin is present, and therefore quassia can be prescribed with salts of iron.

Dose, 2—8 gr. 0·12—0·5 G.

Preparations (B.P.)

1. **Infusum Quassiæ Concentratum.** Quassia, 8 ; alcohol (90 per cent.), 25 ; distilled water, q.s.

Dose, 30—60 min. 2—4 ml.

2. **Infusum Quassiæ.**

Dose, ½—1 fl. oz. 15—30 ml.

3. **Infusum Quassiæ Recens.** Quassia, 1 ; cold water, 100. The water is cold to avoid extracting too much of the bitter principle.

Dose, ½—1 fl. oz. 15—30 ml.

4. **Tinctura Quassiæ.** Quassia ; alcohol (45 per cent.) Macerate.

Dose, 30—60 min. 2—4 ml.

Action and Therapeutics

Apart from its value as a bitter, quassia infusion mixed with an equal quantity of water is used as a colonic wash in cases of infection by *Oxyuris vermicularis ;* its value as an anthelmintic has been overrated.

ORANGE PEEL

Aurantii Cortex Recens (B.P.). Fresh Bitter Orange Peel. The fresh outer part of the pericarp of *Citrus Aurantium.*

Preparations (B.P.)

1. **Tinctura Aurantii.** Fresh bitter orange peel ; alcohol (90 per cent.). Macerate.

Dose, 30—60 min. 2—4 ml.

2. **Syrupus Aurantii.** 3 per cent. concentrated tincture of orange ; syrup.

Dose, 30—120 min. 2—8 ml.

Aurantii Cortex Siccatus (B.P.). Dried Bitter Orange Peel

Preparation **(B.P.)**

1. Infusum Aurantii Concentratum. Dried bitter orange peel; alcohol (25 per cent.).

Dose, 30—60 min. 2—4 ml.

2. Infusum Aurantii.

Dose, ½—1 fl. oz. 15—30 ml.

GROUP IV

Volatile Oils and Cantharidin

The volatile oils are all mildly antiseptic. When applied externally they cause local warmth (**rubefacients**) due to vaso-dilatation, and some may even produce vesication (**vesicants**), or even suppuration (**pustulants**).

The more powerful members of the group produce effects remote from the point of application. This is known as **counter-irritation** and is explained in part by sensory nerve-end stimulation; viz.:

(1) Reflex stimulation of the vital centres in the medulla.

(2) Local effect of vaso-dilatation which acts beneficially when pain from an internal organ is referred to the area of application. The response of the skin to various irritants is a complex one which has been clarified by the work of Lewis. Light stroking causes blanching due to capillary contraction. A firmer stroke, or other more powerful stimulus, provokes the triple response of (1) a red line marking the extent of application of the stimulus. This is due to active dilatation of capillaries and the smallest arterioles and venules. (2) A flare, *i.e.* a diffuse blushing of the neighbouring area due to dilatation of larger arterioles. This develops very quickly on (1). (3) A wheal in the course of the stimulated area due to plasma exudation. Effects (1) and (3) are probably due to liberation of a histamine-like substance. The flare, however, can be abolished by the injection of local anæsthetics, but not by division of the sensory nerves. It seems to depend on the integrity of the sensory nerve

terminations. It is possible that a special system of nerve fibres is responsible to this reaction to injury.

The therapeutic value of such inflammatory skin reaction in an area to which pain is referred is unquestionable. It is probably due to the skin stimulus setting up sensory currents which occupy a common route with the pain impulses originating in the affected viscus. The corresponding spinal segments thus convey both impulses. The stronger the counter-irritation, the more it " crowds-out " the visceral pain.

(3) Effect on distant organs by application of counter-irritants to corresponding skin area. It has been shown that strong stimulation by vesicants causes vaso-dilatation in an internal viscus connected with the skin area through the nervous system alone.

Volatile oils taken internally produce reflex salivation, a feeling of warmth in the stomach, relief of the sensation of distension, and eructation. This is known as **carminative action,** and its value is widely recognized in the taking of liqueurs at the end of a meal. There is some relaxation of the muscle of the stomach and increased peristalsis of the intestines, and ferment activity is retarded. Large quantities produce violent purgation.

In large doses they are gastro-intestinal **irritants.** Their irritation of the stomach reflexly stimulates the heart and the central nervous system. They are absorbed and excreted by the skin, which they may thus irritate, and by the bronchial mucous membrane, which they consequently stimulate, increasing the amount of secretion from it, its vascularity, the expulsive power of its unstriped muscle, and reflexly this irritation leads to coughing ; consequently they are **expectorants.**

The central nervous system is affected by a few of these drugs, the best known being **Thujon** which is contained in absinthe, and **Apiol** which is extracted from parsley. Cerebral stimulation and depression in varying degree is produced by the absorption of large quantities of most of the group.

They are also largely excreted by the kidneys, which are stimulated even to inflammation, and hence these drugs are often **diuretic**; and by the **genito-urinary mucous membrane**, which is also stimulated, often so energetically that it becomes inflamed. Apiol has been used for criminal abortion.

The oils consisting of terpenes are oxidized to phenols, and are excreted in the urine in combination with glycuronic or sulphuric acid.

Some volatile oils act strongly in all these ways; others act much more powerfully in some than in others. They will be classified according to the tissue on which they chiefly act, or for the action for which they are mostly used.

CLASS I. Volatile oils, including camphors, acting chiefly upon, or used chiefly for their stimulation of, the **skin.**

Oil of Turpentine, Cade, Colophony, Camphor, Menthol, Oil of Mustard, Oil of Cajuput, Oil of Eucalyptus, Oil of Rosemary, Arnica Flowers, Myrrh, Sassafras.

CLASS II. Volatile oils acting chiefly upon, or used chiefly for their stimulation of, the **gastro-intestinal tract.**

Cloves, Nutmeg, Cinnamon, Lemon, Pepper, Ginger, Cardamoms, Oil of Lavender, Oil of Peppermint, Anise, Coriander, Fennel, Caraway, Dill, Betel.

CLASS III. Malodorous volatile oils used to stimulate reflexly the **central nervous system.**

Valerian.

CLASS IV. Volatile oils (or substances containing them) acting chiefly upon, or used chiefly for their stimulation of, the **bronchial mucous membrane.**

Terebene, Balsam of Peru, Balsam of Tolu, Storax.

CLASS V. Volatile oils (or substances containing them) acting chiefly upon, or used chiefly for their stimulation of, the **kidneys and genito-urinary tract.**

Oil of Cubebs.

CLASS I. OF Volatile Oils

Those used chiefly for their action on the skin.

OIL OF TURPENTINE

Oleum Terebinthinæ (B.P.). *Synonym.* Rectified Oil of Turpentine. The oil distilled from the oleo-resin exuding from various species of *Pinus* and rectified.

CHARACTERS. Mixes with other volatile and fixed oils. *Solubility.* 1 in 7 of alcohol (90 per cent.), 3 in 10 of ether, and in all proportions in absolute alcohol and chloroform.

COMPOSITION. Oil of turpentine is a mixture of 1. Several isomeric hydrocarbons (*terpenes*). 2. Resin acids. 3. Various oxidation products, *e.g.* camphoric acid.

Doses, 3—10 min. 0·2—0·6 ml.
120—240 min. 8—16 ml. as anthelmintic.

Preparation **(B.P.)**

Linimentum Terebinthinæ. Oil of turpentine, 650; camphor, 50; soft soap; water, to 1000.

Action

External. This oil is **rubefacient, counter-irritant,** and **vesicant.** Like the other volatile oils it is **antiseptic** and **disinfectant.** It is absorbed by the unbroken skin.

Internal. *Alimentary canal.* Oil of turpentine has the same stimulant effect when locally applied to the mouth and pharynx as it has on the skin, and in the stomach it acts as a **carminative** but is seldom used as such on account of its taste. Its effects on the intestine are the same as those on the stomach. A very large amount leads to **purging,** the motions sometimes containing blood. Oil of turpentine is **anthelmintic,** killing the tapeworm when administered in doses of 2 to 4 fl. dr. (8 to 16 ml.); but this treatment may cause severe symptoms. When given as an enema it kills the threadworm and inflames the intestinal mucosa.

Respiration. When inhaled, oil of turpentine acts on the bronchial mucous membrane as it does on the skin, irritating it, dilating the vessels, increasing the secretion, stimulating the muscles of the bronchi, and reflexly exciting cough, so that the drug is a **powerful expectorant.** If given internally, as some of it is excreted by the bronchial mucous membrane, similar effects are produced. At the same time the activity of the respiratory movements is increased from central stimulation.

Nervous system. Oil of turpentine in large doses is a severe depressant to the nervous system, producing languor, dulness, sleepiness, and unsteady gait.

Kidneys. It acts more powerfully on these than almost any other volatile oil. Even moderate doses may lead to pain in the loins, scanty high-coloured urine, albuminuria, and **hæmaturia.** The **urinary passages** are also **irritated**; consequently micturition is painful, and a sensation of heat in the perinæum is present. If a large dose has been given the urine may be completely suppressed. Turpentine causes the urine to smell of violets.

Skin. Small quantities of oil of turpentine are excreted in the sweat, and may cause an erythematous rash.

Excretion. Chiefly urine—some unchanged, some in combination with glycuronic acid ; also sweat, respiratory mucous membranes, milk, bile and, after very large doses, in stools.

Therapeutics

External. Oil of turpentine is employed as a counter-irritant in various forms of chronic inflammation, such as arthritis, bronchitis, or pleurisy.

The Turpentine Stupe is used to relieve abdominal pain and flatulence. Half to one teaspoonful of the oil is sprinkled over a square of flannel which has been wrung out of hot water. It must not be covered by an impermeable material lest vesication results.

Internal. An enema (1 fl. oz., to 15 fl. oz., of mucilage of starch) is efficacious in relieving constipation but it produces considerable inflammation of the mucosa. If it is used as an anthelmintic it is emulsified in mucilage and followed by a dose of castor oil.

OIL OF CADE

Oleum Cadinum (B.P.). *Synonym.* Juniper Tar Oil.

Characters. Dark, reddish-brown, oily liquid of bitter taste.

Action and Therapeutics

The action in the skin is that of other volatile oils. It is used for this stimulant property and its antiseptic power in psoriasis, eczema and pruritus.

COLOPHONY

Colophonium (B.P.). *Synonym.* Resin. The residue left after distillation of oil of turpentine from the oleo-resin of various species of *Pinus.*

Characters. Translucent, yellowish, brittle. Odour and taste like turpentine.

Action and Therapeutics

Resin is antiseptic and slightly stimulant, and is, therefore, an excellent application for indolent ulcers, sores, and wounds.

Certain volatile oils, if allowed to stand in the cold, deposit crystalline substances known as stearoptenes. Of these, only camphor and menthol (Japanese camphor) need be mentioned.

CAMPHOR

Camphora (B.P.). $C_{10}H_{16}O$. A white crystalline substance obtained from *Cinnamomum camphora*, the camphor laurel, and purified by sublimation.

Characters. Colourless, crystalline masses. Taste pungent, bitter, followed by a sensation of cold. Volatilizes slowly at ordinary temperatures. *Solubility.* 1 in 700 in water, 1 in 2 of oil of turpentine, 1 in 4 of olive oil, readily in milk, ether, alcohol, or chloroform.

Dose, 2—5 gr. 0·12—0·3 G.
1—3 gr. 0·06—0·2 G. by subcutaneous injection.

Preparations (B.P.)

1. **Aqua Camphoræ.** Dissolve camphor in alcohol (90 per cent.) and add distilled water. Contains about ½ gr. to 1 fl. oz.

   Dose, ½—1 fl. oz. 15—30 ml.

2. **Linimentum Camphoræ.** *Synonym.* Camphorated Oil. Camphor, in flowers 1 ; oil 4.

3. **Linimentum Camphoræ Ammoniatum.** *Synonym.* Compound Liniment of Camphor. Camphor, 125 ; strong solution of ammonia, 250 ; oil of lavender ; alcohol (90 per cent.), to 1000.

4. Spiritus Camphoræ. Camphor; alcohol (90 per cent.). **Dose, 5—30 min. 0·3—2 ml.** In milk or on sugar, as water precipitates the camphor.

5. Tinctura Opii Camphorata *see* Opium.

Action

External. Camphor, although not a volatile oil, behaves like one, acting both as rubefacient and carminative. Thus it is a direct cutaneous stimulant, dilating the vessels of the skin, and at first causing a sensation of **warmth**, but subsequently a slight degree of local **anæsthesia.** It is a feeble antiseptic.

Internal. *Gastro-intestinal tract.* In the stomach it acts as a carminative.

Absorption and Excretion. It is quickly absorbed, both from the intestines and skin, and is partially oxidized to form camphorol. This substance combines with glycuronic acid and is excreted in the urine as campho-glycuronic acid.

Circulation. Camphor has no direct stimulant action on the heart, but the rate is increased temporarily as the result of reflex stimulation. This effect is trivial. The blood pressure may be slightly raised for the same reason, and also by virtue of stimulation of the constrictor centre. With large doses the pressure falls because of dilatation of peripheral vessels by direct action on their walls. The pulmonary and coronary arteries are also affected in this manner.

Nervous system. The respiratory centre in the medulla is stimulated reflexly and also, after absorption, directly. Five to ten grains will in some persons produce a feeling of exhilaration, or in others a sense of comfort and quietness. Larger doses cause excitement, giddiness, staggering, a slow pulse, and ultimately headache, burning pains in the stomach, faintness, confusion of ideas, delirium, violent convulsions, insensibility, a small feeble pulse, and finally death from collapse. In mammals, including man, camphor acts by first stimulating and subsequently depressing the cerebral cortical areas and the medullary centres.

Therapeutics

External. Its stimulating effects make camphor a favourite ingredient of many liniments. It is used as a mild counter-irritant in, for example, chronic rheumatism, neuralgia, and sciatica.

Internal. It is used as a stimulant in heart failure, being injected subcutaneously as a solution in sterilized olive oil. It has no action on the heart and acts solely by stimulation of the medullary centres.

Leptazolum (B.P.). *Tr. Name.* Cardiazol. It is Pentamethylentetrazol.

Dose, ¾—1½ gr. 50—100 mg.

Preparation (B.P.)

Injectio Leptazoli. Contains 10 per cent. of Leptazol.

Dose, 8—15 min. 0·5—1 ml.—by subcutaneous injection.

Nikethamidum (B.P.) *Tr. Names.* Anacardone; Coramine; Nicamide. It is pyridine-β-carboxylic acid diethylamide.

Dose, 5—15 gr. 0·3—1 G.
4—15 gr. **0·25—1 G.** by subcutaneous, intramuscular or intravenous injection.

Preparation (B.P.)

Injectio Nikethamidi. A 25 per cent. aqueous solution of nikethamide.

Dose, 15—60 min. 1—4 ml.—by subcutaneous, intramuscular or intravenous injection.

Action and Therapeutics

Several compounds, known as *analeptics*, or restoratives, have an effect on the nervous system, especially when the brain is depressed by narcotics, similar to that of camphor. Leptazol, nikethamide, and picrotoxin (*q.v.*) are of this type. Leptazol is chemically related to camphor. It stimulates the higher centres of the cerebrospinal axis chiefly, but the cord is also affected. In large doses it causes convulsions of cerebral and spinal type. Both can be elicited even if the cerebrum is removed above the thalamus. The respiratory, vasomotor, and vagal medullary centres are stimulated. It has no direct effect on the heart or blood vessels, but may be of value in circulatory failure through its stimulation of the medullary centres. It is rapidly absorbed from all sites and quickly destroyed. It is relatively non-toxic. Convulsant doses produce violent clonic and tetanic spasms which may produce fracture of the vertebræ.

It is of great value in **hypnotic poisoning,** especially when due to barbiturates, bromethol, paraldehyde and chloral hydrate. It has been used as a convulsant in the treatment of **schizophrenia** but electroconvulsion therapy is taking its place on account of the danger of spinal fracture.

Nikethamide is a pyridine derivative. It is a water-soluble viscous oil. Its main effect is that of stimulation of the respiratory centres reflexly by action on the chemoreceptors of the carotid body. It has also a direct stimulant effect on the cerebrospinal axis, for in large doses it will cause convulsions. It has no direct effect on the heart.

It is of value in **morphine poisoning** and in combating other respiratory depressants.

MENTHOL

Menthol (B.P.). $C_{10}H_{20}O$. A crystalline substance obtained by cooling the oil distilled from various species of *Mentha.*

CHARACTERS. Colourless acicular crystals. Odour and taste of peppermint. *Solubility.* Very sparingly in water or glycerin, 5 in 1 of alcohol (90 per cent.), 4 in 1 of chloroform, 1 in 4 of olive oil.

Dose (not official), ½—2 gr. 0·03—0·12 G.

Action and Therapeutics

External. Menthol is an antiseptic and also a mild local anæsthetic. When rubbed on the skin it produces vaso-dilatation and rise of local temperature accompanied by a sensation of cold which must be due to differential stimulation of sensory nerve-endings. This is soon followed by numbness. Its local application is often efficacious in relieving frontal headache. The local application of menthol often relieves itching. A mixture for *pruritus ani* consists of menthol, 1 part, eucalyptol, 2 parts, sodium biborate, sodium bicarbonate, powdered alum, each 8 parts.

Menthol is readily volatilized by the addition of hot water, and it, in conjunction with various volatile oils, can be thus inhaled in cases of coryza, tracheitis, and sinusitis. In such maladies it is helpful in clearing the nasal passages.

Internal. Its use as a carminative has been abandoned, as it easily upsets digestion.

Excretion. It is excreted in the urine as menthoglycuronic acid, rendering it aseptic and giving it a pleasant smell.

MUSTARD OIL

Oleum Sinapis Volatile (**B.P.C.**). The volatile oil distilled from black mustard seeds.

Preparation (**B.P.C.**)

Linimentum Sinapis. Volatile oil of mustard, 35; camphor, 55; castor oil, 125; alcohol (90 per cent.), to 1000.

Action

External. Mustard oil is a typical powerful local **irritant,** and produces blistering, and destruction of the underlying tissues. It should be used for its rubefacient action only.

Crude mustard is safer for use because the oil is formed slowly from it when it is moistened.

Internal. *Gastro-intestinal tract.* Mustard also acts here as an irritant. Gastroscopic observations have shown that the introduction of mustard diluted to four times the usual strength as a condiment produces intense inflammatory reaction in the mucosa. A dose of one to four teaspoonfuls stirred up in a tumbler of water is sufficiently irritating to be a direct stomachic **emetic.**

Therapeutics

External. A poultice made with linseed and having a little mustard (1 part to 16 of linseed) sprinkled on it is an efficacious counter-irritant. The mustard leaves that are sold, moistened in water, form a convenient application.

Common colds and febrile conditions, especially in children, are treated by placing the feet and legs or the whole body in mustard and warm water (10 to 15 ounces of ordinary mustard to every 15 gallons of water, as hot as can be borne), the object being by the cutaneous dilatation to withdraw blood from the inflamed part.

Internal. Mustard is used as a condiment, and also as an **emetic**. It is especially valuable for poisoning by narcotics, because of its reflex stimulant effects.

CAJUPUT OIL

Oleum Cajuputi (B.P.). The oil distilled from the leaves of *Melaleuca leucadendron.*

CHARACTERS. A very volatile, bluish-green liquid, with a camphoraceous odour. Taste camphoraceous, and succeeded by a sensation of coldness. Readily soluble in alcohol.

Dose, 1—3 min. 0·06—0·2 ml.

Preparation (B.P.)

Spiritus Cajuputi. Oil of cajuput ; alcohol (90 per cent.).
Dose, 5—30 min. 0·3—2 ml.

Therapeutics

EXTERNAL. Cajuput oil is used as a counter-irritant—usually diluted with sweet oil.

INTERNAL. It is given on sugar as a remedy for flatulence.

OIL OF EUCALYPTUS

Oleum Eucalypti (B.P.). The oil distilled from the fresh leaves of various species of Eucalyptus.

Dose, 1—3 min. 0·06—0·2 ml.

Preparations

Eucalyptol (B.P.). $C_{10}H_{18}O$. *Synonym.* Cineole.

CHARACTERS. Colourless liquid of aromatic odour and pungent taste.

Dose, 1—3 min. 0·06—0·2 ml.

Unguentum Eucalypti (B.P.C.). Oil of eucalyptus, 1: white soft paraffin, 5 ; hard paraffin, 4.

Action

EXTERNAL. Oil of eucalyptus is less irritant when applied externally than other volatile oils, but if its vapour is confined it will produce vesication and pustulation. It has the antiseptic properties of this group. Eucalyptol is less irritating than the oil.

INTERNAL. That of the group.

Therapeutics

Eucalyptus may be used for the same purposes as those of the group. Inhalation of its vapour is a popular remedy for coryza. Eucalyptol is most suitable if used in a spray for this purpose.

OIL OF ROSEMARY

Oleum Rosmarini (B.P.). The oil distilled from the flowering tops of *Rosmarinus officinalis.*

CHARACTERS. A colourless or pale yellow volatile oil. Pungent odour ; camphoraceous taste.

Action and Therapeutics

That of other aromatic volatile oils. It is commonly used to give a pleasant scent to hair lotions and other preparations which are used externally.

MYRRH

Myrrha (B.P.). An oleo-gum-resin obtained from the stem of *Commiphora molmol* and other species.

Preparation (B.P.)

Tinctura Myrrhæ. Myrrh ; alcohol (90 per cent.). Macerate.

Dose, 30—60 min. 2—4 ml.

Action

Both externally and internally myrrh has the same actions as other substances containing a volatile oil.

Therapeutics

INTERNAL. It is, in the form of ½ fl. dr. (2 ml.) of the tincture diffused through 1 fl. oz. (30 ml.) of water, used as a mouth wash and gargle for sore throat and aphthous stomatitis. It is frequently given with purgatives for the sake of its carminative properties.

SASSAFRAS OIL

Oleum Sassafras (B.P.C.). *Synonym.* Oil of Sassafrax.

Dose, 1—5 min. 0·06—0·3 ml.

Action and Therapeutics

Carminative and astringent. Used extensively locally for destruction of pediculi and their nits. Also used for *rhus dermatitis.*

CLASS II. OF Volatile Oils

Those used chiefly for their action on the gastro-intestinal tract.

CLOVES

Caryophyllum (B.P.). Cloves. The dried flower-buds of *Eugenia aromatica.*

Preparations (B.P.)

1. **Infusum Caryophylli Concentratum.** Cloves; alcohol (25 per cent.).

Dose, 30—60 min. 2—4 ml.

2. **Infusum Caryophylli.**

Dose, ½—1 fl. oz. 15—30 ml.

Cloves are contained in Pulvis Cretæ Aromaticus.

Oleum Caryophylli (B.P.). Oil of Clove. The oil distilled from cloves.

CHARACTERS. Easily soluble in spirit or ether.

Dose, 1—3 min. 0·06—0·2 ml.

Oil of cloves is contained in Pilula Colocynthidis et Hyoscyami.

Therapeutics of Cloves and Oil of Cloves

The oil in a paste is used as a soothing, antiseptic, temporary filling for a cavity prepared by drilling of a carious tooth. Cloves are frequently employed in cookery for their taste, and because they stimulate the appetite and aid digestion. The oil or the infusion may be used medicinally as a carminative, or as an antispasmodic. It will have been noticed that oil of cloves is present in a pill containing colocynth. This is to prevent griping.

NUTMEG

Myristica (B.P.). Nutmeg. The dried kernel of the seed of *Myristica fragrans.*

Oleum Myristicæ (B.P.). Volatile oil of nutmeg. The oil distilled from nutmegs.

CHARACTERS. Colourless or pale yellow. Odour and taste of nutmeg.

Dose, 1—3 min. 0·06—0·2 ml.

Action and Therapeutics

That of other aromatic oils.

CINNAMON

Cinnamomum (B.P.). The dried inner bark of shoots of the cultivated cinnamon tree, *Cinnamomum zeylanicum.*

Oleum Cinnamomi (B.P.). The oil distilled from cinnamon bark.

Characters. Yellowish, becoming cherry-red on keeping.

Dose, 1—3 min. 0·06—0·2 ml.

Preparation (B.P.)

Aqua Cinnamomi Concentrata. Oil of Cinnamon, 1; alcohol (90 per cent.), 30; distilled water, 1000.

Dose, 5—15 min. 0·3—1 ml.

Action and Therapeutics

Those of other aromatic volatile oils.

LEMON

Limonis Cortex Recens (B.P.). Fresh Lemon Peel. The fresh outer part of the pericarp of the fruit of *Citrus Limonia.*

Preparations (B.P.)

1. **Syrupus Limonis.** Lemon peel, 60; alcohol (60 per cent.), 9·5; citric acid; syrup to 1000.

Dose, 30—120 min. 2—8 ml.

2. **Tinctura Limonis.** Lemon peel; alcohol (60 per cent.). Macerate.

Dose, 30—60 min. 2—4 ml.

Limonis Cortex Siccatus. Dried Lemon Peel. It is contained in Infus. Gent. Co. Conc.

Oleum Limonis (B.P.). The oil obtained from fresh lemon peel.

Action and Therapeutics

The same as those of orange. The oil applied externally is rubefacient.

PEPPER

Capsicum (B.P.). The dried ripe fruit of *Capsicum minimum.* Dried and powdered it constitutes red pepper.

Preparations (B.P.)

1. **Tinctura Capsici.** Capsicum; alcohol (60 per cent.). Macerate.

Dose, 5—15 min. 0·3—1 ml.

2. **Unguentum Capsici.** Capsicum; hard paraffin; soft paraffin; prepared lard.

In India prepared suet should be used instead of prepared lard.

Action

That of volatile oils generally.

Therapeutics

External. Capsicum ointment is used as a counter-irritant. Unguentum Capsici Co. (**B.P.C.**) is the same as the well-known Chillie paste and is an excellent counter-irritant. Equal parts of Tincture of Capsicum and Compound Liniment of Camphor are painted on unbroken chilblains. Wool impregnated with capsicum is applied in chronic rheumatism.

Internal. It is used as a condiment. Medicinally it is given as a carminative.

GINGER

Zingiber (B.P.). The scraped and dried rhizome of *Zingiber officinale.*

Dose, 5—15 gr. 0·3—1 G.

Preparations (**B.P.**)

1. **Syrupus Zingiberis.** Powdered ginger; alcohol (90 per cent.); syrup.

Dose, 30—120 min. 2—8 ml.

2. **Tinctura Zingiberis Fortis.** Ginger; alcohol (90 per cent.). Five times strength of (3).

Dose, 5—10 min. 0·3—0·6 ml.

3. **Tinctura Zingiberis Mitis.** Strong tincture of ginger 1; alcohol (90 per cent.), to 5.

Dose, 30—60 min. 2—4 ml.

Action and Therapeutics

Its action is the same as that of other substances containing aromatic volatile oils. It is chiefly used as a carminative, and flavouring agent.

CARDAMOMS

Cardamomum (B.P.). Cardamom Seeds. The dried ripe seeds of *Elettaria cardamomum.* Malabar.

Composition. The chief constituent is a volatile oil.

Dose, 10—30 gr. 0·6—2 G.

Preparation (**B.P.**)

Tinctura Cardamomi Composita. Cardamoms, 14; caraway, 14; cinnamon, 28; cochineal; glycerin; alcohol (60 per cent.), to make 1000. Macerate.

Dose, 30—60 min. 2—4 ml.

Action and Therapeutics

The compound tincture is used as a carminative and colouring agent. Tinctura Cardamomi Aromatica (Tr. Carminativa) **B.P.C.** (Dose, 2 to 10 min.—0·12 to 0·6 ml.) is a popular carminative containing cardamoms, strong tincture of ginger, oil of cinnamon, oil of caraway, oil of cloves and rectified spirit.

OIL OF LAVENDER

Oleum Lavandulæ (B.P.). The oil distilled from the flowers of *Lavandula officinalis.*

Action and Therapeutics

It is an ingredient of Lin. Camph. Ammon.

OIL OF PEPPERMINT

Oleum Menthæ Piperitæ (B.P.). The oil distilled from the fresh flowering peppermint, *Mentha piperita.*

Composition. The chief constituents are—(1) *Menthol.* (2) Menthone, a liquid terpene. (3) Menthyl acetate.

Dose, 1—3 min. 0·06—0·2 ml.

Preparations (B.P.)

1. **Aqua Menthæ Piperitæ Concentrata.** Oil of peppermint, 2 ; alcohol, 60 ; distilled water to 100.

Dose, 5—15 min. 0·3—1 mil.

2. **Emulsio Menthæ Piperitæ.** Oil of peppermint, 10 per cent. ; liquid extract of quillaia, water. Oil of peppermint content is equivalent to that of Spirit. Menth. Pip.

Dose, 5—30 min. 0·3—2 ml.

3. **Spiritus Menthæ Piperitæ.** Oil of peppermint, 1 ; alcohol, 9.

Dose, 5—30 min. 0·3—2 ml.

Action and Therapeutics

The action of oil of peppermint is the same as that of volatile oils generally, but the cool numb feeling often produced by volatile oils after the sensation of warmth has passed off is especially well marked with oil of peppermint, and this effect, which is due to the menthol in it, has caused it to be applied externally in neuralgia.

ANISE

Anisum (B.P.C.). Anise Fruit. The dried ripe fruit of *Pimpinella Anisum.*

Oleum Anisi (B.P.). The volatile oil, distilled from the anise fruit.

COMPOSITION. The chief constituent is Anethole, 85 per cent., $C_{10}H_{12}O$.

Dose, 1—3 min. 0·06—0·2 ml.

Action and Therapeutics

The action of oil of anise is the same as that of aromatic oils generally. It is specially used for flatulence in children.

CORIANDER FRUIT

Coriandrum (B.P.). The dried ripe fruit of *Coriandrum sativum.*

COMPOSITION. The chief constituent is the official *volatile oil (see below).*

Oleum Coriandri (B.P.). A volatile oil distilled from the fruit.

Dose, 1—3 min. 0·06—0·2 ml.

Action and Therapeutics

That of other volatile oils.

FENNEL FRUIT

Fœniculum (B.P.). The dried ripe fruit of cultivated plants of *Fœniculum vulgare.*

COMPOSITION. The chief constituent is a volatile oil.

It is an ingredient of Compound Liquorice Powder.

Action and Therapeutics

Those of the group.

CARAWAY FRUIT

Carum (B.P.). Caraway Fruit. The dried ripe fruit of *Carum carvi.*

Oleum Cari (B.P.). The oil distilled from caraway fruit and rectified.

Dose, 1—3 min. 0·06—0·2 ml.

Action and Therapeutics

Those of other aromatic volatile oils.

DILL FRUIT

Anethum (B.P.). The dried ripe fruit of *Anethum graveolens.*

Preparations (B.P.)

1. **Aqua Anethi Concentrata.** Oil of dill, 2; alcohol; distilled water, to 100.

Dose, 5—15 min. 0·3—1 ml.

Oleum Anethi (B.P.). The oil distilled from the dill fruit.

Characters. Pale yellow. Odour pungent. Taste hot and sweetish.

Dose, 1—3 min. 0·06—0·2 ml.

Action and Therapeutics

Dill water is a popular remedy for intestinal colic in infants.

BETEL

Betel (B.P.C.). The dried leaves of *Piper Betel.*

Characters. Leaves 15 centimetres long containing a brown aromatic oil.

Note. Betel nut and Areca nut are the same, being the nut of *Areca catechu*, one of the palms. It contains several alkaloids.

Uses

In India and Malay natives indulge in the habit of chewing betel leaves. White or black catechu and areca nut (betel nut), mixed with various spices and aromatics, are wrapped up in betel leaves which have been previously smeared with a little chunam or shell lime, and little masses of this mixture are chewed.

CLASS III. OF Volatile Oils

Malodorous oils used to stimulate reflexly the nervous system.

VALERIAN

Valeriana (B.P.). Valerian Rhizome.

Preparation (B.P.)

Tinctura Valerianæ Ammoniata. Powdered valerian, 200; oil of nutmeg; oil of lemon; solution of ammonia, 100; alcohol (60 per cent.), 900. Macerate.

Dose, 30—60 min. 2—4 ml.

Action and Therapeutics

Valerian acts in virtue of its volatile oil, which has the same properties as other volatile oils.

Preparations of valerian are prescribed for hysteria and other neurotic conditions, and sometimes with benefit. Probably the result is referable to the mental impression produced by the unpleasant smell.

CLASS IV. OF Volatile Oils

Used chiefly for action on bronchial mucous membrane.

TEREBENE

Terebenum (B.P.C.). Terebene. A mixture of dipentene and other hydrocarbons produced by agitating oil of turpentine with successive portions of sulphuric acid.

Terpini Hydras (B.P.C.).

Dose, 3—10 gr. 0·2—0·6 G.

Action and Therapeutics

They stimulate the bronchial mucous membrane during excretion and act also as mild antiseptics. Given by mouth or by inhalation for cases of chronic bronchitis.

Terpineol (B.P.). $C_{10}H_{18}O$. Derived from Terpin hydrate. Colourless liquid with lilac odour. Used to disguise the odour of iodoform.

BALSAM OF PERU

Balsamum Peruvianum (B.P.). A balsam exuded from the trunk of *Myroxylon Pereiræ.*

CHARACTERS. A liquid viscid as treacle, orange or reddish-brown, and transparent. Taste disagreeable, burning. *Solubility.* Insoluble in water, easily in chloroform, and in 1 of alcohol (90 per cent.).

Action and Therapeutics

An antiseptic expectorant but is seldom used internally. It may be employed in the form of an ointment for bedsores and chilblains.

BALSAM OF TOLU

Balsamum Tolutanum (B.P.). A balsam which on incision exudes from the trunk of *Myroxylon toluifera.*

CHARACTERS. A reddish-yellow, soft, tenacious solid, becoming hard by keeping and brittle in the cold. Very fragrant odour. Taste aromatic. *Solubility.* Easily in alcohol (90 per cent.), not in water.

Preparations (B.P.)

1. **Syrupus Tolutanus.** Balsam of Tolu, 25; sugar; water to make 1000 (contains only the aromatic constituents, the resinous portion is insoluble in syrup).

Dose, 30—120 min. 2—8 ml.

2. Tinctura Tolutana. Balsam of Tolu, 1; alcohol, 10. Dissolve.

Dose, 30—60 min. 2—4 ml. The balsam of tolu is precipitated by adding water, therefore it should be suspended with mucilage.

Action and Therapeutics

An antiseptic expectorant used for bronchitis. Also employed as a flavouring agent.

STORAX

Styrax Præparatus (B.P.). Prepared Storax. A viscid balsam obtained from the wounded trunk of *Liquidambar orientalis*.

CHARACTERS. A brownish-yellow, semi-transparent, semi-fluid balsam. Odour strong, agreeable.

Action and Therapeutics

Storax has just the same action as balsams of Tolu and Peru and benzoin, and may be employed for the same purposes.

CLASS V. OF Volatile Oils

Now rarely used for action on the kidneys and genito-urinary tract.

CUBEBS

Cubeba (B.P.C.). Cubeb. The dried unripe full-grown fruit of *Piper cubeba*.

Dose, 30—60 gr. 2—4 G.

Preparation (B.P.C.)

Tinctura Cubebæ. Cubebs, 1; alcohol (90 per cent.), 5. Percolate.

Dose, 30—60 min. 2—4 ml.

Oleum Cubebæ (B.P.C.).

SOURCE. The volatile oil distilled from cubebs.

CHARACTERS. Colourless or greenish-yellow, with the odour and taste of cubebs.

Dose, 5—20 min. 0·3—1·2 ml.—suspended in mucilage.

Action and Therapeutics

The action and uses of the group but especially as diuretic and urinary antiseptic. It appears in the urine in a form (probably as a salt of cubebic acid) which may be precipitated by nitric acid.

GROUP V

Digestive Ferments

Pepsin, Pancreatin, and Diastase

PEPSIN

Pepsinum (B.P.). An enzyme obtained from the fresh and healthy stomach of a pig, sheep, or calf.

CHARACTERS. A light yellow-brown powder, or pale yellow translucent grains or scales. Odour faint. Taste slightly saline. Soluble in water.

Pepsin, in 6 hours, dissolves 2500 times its weight of coagulated white of egg.

Dose, 5—10 gr. 0·3—0·6 G.

Glycerinum Pepsini (B.P.C.). Contains 10 per cent. of pepsin in hydrochloric acid, glycerin and water.

Dose, 60—120 min. 4—8 ml.

Action and Therapeutics

The action of pepsin is to convert proteins to peptones in acid media. In an alkaline medium it is inert and rapidly destroyed.

There is seldom any justification for its use, for it is present even in those forms of dyspepsia associated with deficient hydrochloric acid in the gastric juice, except in Addison's (pernicious) anæmia. In advanced achlorhydric (microcytic) anæmia the amount of pepsin may be reduced. It may be used in combination with hydrochloric acid in these diseases, and it may also be employed to predigest food for duodenal feeding.

PANCREATIN

Pancreatinum (B.P.). A buff-coloured powder containing a mixture of enzymes obtained from the pancreas of certain animals. Soluble in water.

Dose, 3—10 gr. 0·2—0·6 G.

Liquor Pancreatini (B.P.C.). Glycerin of pancreatin (1 in 6) with sodium bicarbonate.

Dose, 30—120 min. 2—8 ml.

Action and Therapeutics

Pancreatin in alkaline or neutral media digests protein, converts starch into sugar, and saponifies fats. Pancreatin is used to predigest food, 5 grs. being added to 1 pint of milk heated to 38° C. and maintained at this temperature for 15 minutes. It is then boiled to destroy the ferments. The liquor is given soon after meals, or pancreatin is administered in capsules, to avoid as far as possible the destructive action of free hydrochloric acid in the stomach. It is used to assist pancreatic digestion. As no condition apart from gross disease of the pancreas is known to exist in which pancreatic digestion is deficient the use of these preparations has fallen into abeyance.

DIASTASE

Diastasum (B.P.C.). A mixture containing amylolytic enzymes obtained from malt (*q.v.*).

Characters. Yellowish-white, tasteless powder. Destroyed by heat. Soluble in water.

Dose, 1—5 gr. 0·06—0·3 G.

Action and Therapeutics

Diastase converts starch into dextrin and maltose, and is capable of thus transforming fifty times its own weight of starch.

Taka-Diastase, of similar physical characters, is obtained by the action of a fungus, *Aspergillus oryzae,* upon rice. It is at least twice as powerful as diastase.

The action of the diastases is inhibited by acid over 0·1 per cent., and it is doubtful whether they can be of much use, particularly as absence of pancreatic diastase must be a very rare condition.

They have been used in cases of carbohydrate dyspepsia.

GROUP VI

Purgatives

Salines, Castor Oil, Anthracenes, Phenolphthalein, Sulphur, Jalap—Croton Group

Although many drugs will produce evacuation of the bowels, those which are commonly employed as purgatives are chosen because their action is almost entirely exerted upon the intestines, and they are not liable to rapid absorption, or to the production of remote effects.

The old classification into laxatives, purgatives and drastic purgatives is unsatisfactory because any of these drugs if given in sufficient amount may cause violent evacuation and tenesmus. Division based upon the mode of action is more suitable and will be used here.

(A) Purgatives acting by increasing the bulk of intestinal contents

1. **Unabsorbable food residue ; Cellulose.** This is present in considerable quantity in wholemeal bread, vegetables and fruit.

2. **Agar-Agar.** A dried mucilaginous substance extracted from various algæ. It swells up in the intestine owing to the absorption of much water.

Agar (B.P.). Dose, 60—240 gr. 4—16 G.

3. **Salines.** Certain slowly diffusible salts, *e.g.* salts of magnesium and the sulphate and tartrate of sodium, retain fluid in the bowel and thus increase the bulk of contents. Very watery stools are thus produced, the action being on the small and large intestine. It is a mistake to give concentrated solutions of saline purgatives because they induce pyloric closure; whereas isotonic solutions enter the gut rapidly.

(B) Lubricants

Liquid paraffin (*q.v.*) acts by softening the fæcal mass and, if given in excess, defeats its own object. Thus an unduly soft stool fails to stimulate peristalsis.

(C) Irritants

Under this heading fall the majority of purgatives in common use, all these drugs irritating the mucosa and, therefore, rendering it unduly sensitive to physiological stimuli.

1. **Castor oil,** though a bland substance in itself, is hydrolysed by lipase in the small intestine and glycerol and ricinoleic acid are freed. It is to the irritant action of the latter that the oil owes its efficacy. The effect is exerted upon the small intestine, a fact which accounts for purgation following administration in three to four hours.

2. **Anthracene purgatives,** *e.g.* rhubarb, senna, aloes and cascara sagrada, owe their action to the presence of derivatives of anthracene ($C_{14}H_{10}$), of which emodin is the most important. Purgation is also produced by hypodermic administration of the active principles which are all renal irritants. If absorbed, they tend

to excite uterine contractions (this applies particularly to aloin) and they should, therefore, be used with care in pregnant women.

The action of the anthracene purgatives is exerted on the large intestine only, defæcation occurring as a rule in half to one hour after their entrance into the cæcum. The interval between administration and purgation is seven to eight hours, and for this reason it is usual to prescribe the anthracene purgatives for use at bedtime.

3. **Phenolphthalein** has a similar action to that of the preceding group in that its effect is but slight on the small intestine, but chiefly on the large gut. It is soluble in the bile and alkaline contents of the intestine and then acts as a mild irritant. Purgation also follows subcutaneous injection because it passes into the bile and so attains the lumen of the alimentary tract. Some is absorbed from the large intestine and consequently reappears in the duodenum in the bile. Its effect is thus prolonged over two to three days in diminishing intensity.

4. **Sulphur** owes its action to the production of sulphides in the intestine (*q.v.*). Its chief effect is exerted on the colon.

5. **Jalap, Colocynth and Croton Oil Group.** The members of this group, also known as hydragogue cathartics, are very powerful purgatives, usually owing to the presence of irritant glucosides, *e.g.* convolvulin in jalap, podophyllotoxin in podophyllum. Croton oil contains an irritant resin dissolved in oil which is inert. It is the most powerful of all the purgatives. The whole of the group acts on the small and large intestines, purgation occurring in one to four hours. Delayed action due to obstruction imperils the wall of the gut because the drugs are so irritant.

6. **Mercurial purgatives.** Mercury mixed with chalk (grey powder) and calomel are valuable purgatives, because owing to their insolubility they do not present the dangers inherent in the mercury salts, which are easily absorbed. A small amount of calomel is converted into a soluble form in the small intestine and

this causes sufficient irritation to produce evacuation. The action is on both small and large gut and, judging by the time of action, and tendency to griping, it is probably chiefly on the colon. Difference of opinion exists on this point. It causes no increase in the flow of bile, the green colour of the stools being due to mercury sulphide. (*See also* Mercury.)

(D) Neuro-muscular Stimulants

This group contains such drugs as pituitary extract, physostigmine and thyroid extract. Their action on the gut is quite different from that of the previous groups and is mentioned under the appropriate headings.

None of the purgatives acts as a true cholagogue, *i.e.* there is no increase in bile formation. Magnesium sulphate induces expulsion of bile from the gall bladder, and the jalap-colocynth group, whose action is much enhanced by the presence of bile, appears to have a similar though less certain effect.

All powerful purgatives tend to be followed by atony of the gut wall and consequent constipation, but this is most marked after castor oil and rhubarb (because of tannic acid content).

Rhubarb and less often senna render the urine deep yellow, due to the excretion of chrysophanic acid. Phenolphthalein produces a purple colour if the urine is alkaline.

In connection with purgatives, it should be borne in mind that the production of watery stools implies the presence of a large quantity of liquid matter in the large intestine. This abnormal state of affairs allows of the multiplication of bacteria and the absorption of various toxic bodies into the circulation, and may produce symptoms which will disappear only with cessation of aperient treatment.

Section 1

Saline Purgatives

It has been seen that saline purgatives depend for their action on the fact that they are slowly diffusible, and their osmotic pressure prevents the absorption of fluid even after they have become isotonic with the body fluids. Increased bulk thus induces peristalsis, and evacuation is watery. If both fractions of a salt have the above-mentioned physical characters, it will be more powerfully purgative than if only the anion or kation be thus equipped. For instance, the magnesium ion is absorbed very slowly, and this accounts for magnesium sulphate being the most powerful member of this group. Of acid radicals, sulphates, phosphates, tartrates and citrates are the most important. Sodium sulphate is less powerful than magnesium sulphate because sodium is readily absorbed.

The saline cathartics do not produce purgation when injected hypodermically.

If the urge to defæcation be resisted, the salts are gradually absorbed and, being excreted in the urine, act as diuretics.

Magnesium Salts

1. Magnesii Sulphas (B.P.). Magnesium Sulphate. $MgSO_4,7H_2O$. *Synonym.* Epsom salts.

Characters. Minute colourless rhombic prisms of bitter taste. *Solubility.* 1 in 1·5 of water.

Dose, 30—240 gr. 2—16 G.

Preparations (B.P.)

1. Mistura Magnesii Hydroxidi. *Synonym.* Cream of Magnesia. A mixture of magnesium hydroxide in an aqueous suspension of hydrated magnesium oxide.

Dose, 60—240 min. 4—16 ml.

2. Mistura Sennæ Composita. *Synonym.* Black draught. Contains magnesium sulphate, 250 ; liquid extract of liquorice, 50 ; infusion of senna, q.s.

Dose, 1—2 fl. oz. 30—60 ml.

2. Magnesii Carbonas Ponderosus (B.P.). Heavy Magnesium Carbonate. $(MgCO_3)_3$, $Mg(OH)_2$, $4H_2O$.

Characters. A white granular powder, feebly soluble in water ; 3½ times as heavy as the light carbonate.

Dose, 10—60 gr. 0·6—4 G.

Preparation (B.P.)

Liquor Magnesii Bicarbonatis. *Synonym.* Fluid magnesia. Carbonic acid gas under a pressure of three atmospheres is passed into a mixture of freshly prepared magnesium carbonate and distilled water. It is kept securely corked. *Characters.* A clear effervescing fluid. *Strength.* 7·5 gr. of the carbonate in 1 fl. oz. or 1 G. in 60 millilitres.

Dose, 1—2 fl. oz. 30—60 ml.

3. Magnesii Carbonas Levis (B.P.). Light Magnesium Carbonate. $(MgCO_3)_3$, $Mg(OH)_2$, $4H_2O$.

CHARACTERS. A very light white powder. Partly amorphous, with slender microscopic prisms intermixed. Very insoluble.

Dose, 10—60 gr. 0·6—4 G.

4. Magnesii Oxidum Ponderosum (B.P.). Heavy Magnesia. MgO. *Synonyms.* Heavy calcined magnesia, Heavy magnesium oxide.

CHARACTERS. A white powder, very insoluble in water, 3½ times as heavy as the light.

Dose, 10—60 gr. 0·6—4 G.

5. Magnesii Oxidum Leve (B.P.). Light Magnesia. MgO. *Synonyms.* Light calcined magnesia, Light magnesium oxide.

CHARACTERS. A light bulky white powder, feebly soluble.

Dose, 10—60 gr. 0·6—4 G.

6. Magnesii Phosphas (B.P.C.). *Synonym.* Tribasic magnesium phosphate.

CHARACTERS. Dry, gritty, powder ; insoluble in water.

Dose, 15—60 gr. 1—4 G.

7. Magnesii Trisilicas (B.P.).

CHARACTERS. White, slightly hygroscopic, insoluble powder.

Dose, 5—30 gr. 0·3—2 G.

Action of Magnesium Salts

External. None.

Internal. *Stomach and Intestines.* Magnesia and the magnesium carbonate are antacid. They are both decomposed by the gastric juice, the chloride of magnesium being formed. The carbonic acid in the intestine may dissolve part of this, forming the bicarbonate. These, or the sulphate if that has been taken, act in the intestine as typical **saline purgatives.**

Blood and Urine. Like other alkaline remedies, these magnesium salts, except magnesium sulphate, increase the alkalinity of the blood, alkalize the urine, and are **diuretic.** In the case of the sulphate the alkali reserve of the body is reduced owing to some of the acid radicle combining with alkali and being absorbed and excreted as sodium sulphate. The corresponding magnesium fraction passes on through the gut.

Nervous System. Large doses given intravenously are powerful depressants to the whole nervous system, an action immediately abolished by calcium.

Therapeutics of Magnesium Salts

External. Made into a paste with glycerin (5·5 parts), magnesium sulphate (4·5 parts) is used in the dressing of **boils** and carbuncles. The paste is powerfully hygroscopic and induces separation of slough.

Internal. Magnesia and the carbonate are used as antacids, usually in combination with calcium carbonate, especially in the treatment of duodenal ulcer. The calcium salt checks the tendency to diarrhœa induced by the magnesium. Magnesium phosphate is used in conjunction with the corresponding calcium salt for the same purpose. It is of great value as an antacid which does not produce eructation or alkalosis. Magnesium trisilicate ($Mg_2Si_3O_8$) in 90 gr. doses is an excellent antacid also possessing the above advantages. It neutralizes largely by the formation of the chloride and partly by adsorption of free HCl. It is used in the treatment of **peptic ulcer.**

Fluid magnesia is an excellent aperient for children. The sulphate is largely used, especially for **constipation** associated with hepatic disorder. It is a valuable purgative for use in cases of dropsy. A concentrated solution, if introduced into the duodenum through a rubber tube, causes rapid expulsion of bile from the gall-bladder. The bile so obtained can then be recovered for estimation of the condition of the gall-bladder. The actual drainage of this organ is helpful in the treatment of **cholecystitis.** The effect is less certain when the salt is administered per os.

Nervous System. For tetanus 5 c.c. of 25 per cent. solution of magnesium sulphate have been given intrathecally.

To reduce **Intracranial pressure** in eclampsia, convulsions of acute nephritis, and cerebral tumour, hypertonic magnesium sulphate may be given intramuscularly or per rectum. It should be noted that a 6·5 per cent. solution is isotonic with body fluids: a hypertonic solution should be not less than 25 per cent. It is preferable to employ the rectal route otherwise the depressant action of magnesium on the central nervous system may predominate and even be dangerous: ½ oz. in 6 oz. of water can be given daily. For eclampsia 40 c.c. of 15 per cent. solution (6 grms.) are injected intramuscularly at 6-hour intervals, usually in alternation with morphine.

Sodium Salts

1. Sodii Phosphas (B.P.). Sodium Phosphate. $Na_2HPO_4, 12H_2O$. *Synonym* Di-Sodium Hydrogen Phosphate.

CHARACTERS. Transparent, colourless, efflorescent rhombic prisms. Taste, mildly saline. *Solubility.* 1 in 7 of cold water.

Dose, 30—240 gr. 2—16 G.

2. Sodii Phosphas Exsiccatus. *Synonym.* Anhydrous Sodium Phosphate. Na_2HPO_4.

Dose, 10—75 gr. 0·6—5 G.

3. Sodii Sulphas (B.P.). Sodium Sulphate. $Na_2SO_4,10H_2O$. *Synonym.* Glauber's salts.

CHARACTERS. Colourless, monoclinic transparent prisms, efflorescing on exposure to air. Neutral; taste, saline. *Solubility.* 1 in 3 of water.

Dose, 30—240 gr. 2—16 G.

4. Sodii Sulphas Exsiccatus (B.P.). Na_2SO_4.

CHARACTERS. Hygroscopic white powder. *Solubility.* 1 in 8 of water.

Dose, 15—120 gr. 1—8 G.

5. Sodii et Potassii Tartras (B.P.). Sodium Potassium Tartrate. $NaKC_4H_4O_6,4H_2O$. *Synonyms.* Potassii et Sodii Tartras, Rochelle salt.

CHARACTERS. Large, colourless, neutral, trimetric prisms. Taste like common salt. *Solubility.* 1 in 1·5 of cold water.

Dose, 120—240 gr. 8—16 G.

Preparation (B.P.)

Pulvis Effervescens Compositus. *Synonym.* Seidlitz powder. Take tartarated soda 7·5 G. and sodium bicarbonate 2·5 G.; mix and wrap in blue paper. Tartaric acid 2·5 G., wrapped in white paper.

Dose. Dissolve the powder in the blue paper in nearly half a pint of cold or warm water, and then add that in the white paper, and drink while effervescing.

Action

That of saline cathartics.

Therapeutics

Internal. They are used as **aperients** and are slightly less powerful than the corresponding magnesium salts.

The sulphate is the most powerful purgative of the sodium salts. It is the chief constituent of Carlsbad, Marienbad, Tarasp, and Condal waters, and it occurs associated with much sulphate of magnesium in Æsculap, Hunyadi János, Seidlitz, Pullna, Friedrichshall, Rubinat, Apenta, and Kissingen waters. The phosphate is a milder and less unpleasant purgative than the others; it is often given to children. The effervescing preparations are palatable forms.

Large doses make the evacuations very watery, and are useful to remove fluid in dropsy or ascites. Sodium sulphate is a powerful diuretic if administered intravenously in 4·28 per cent. solution. It is usually given by drip in cases of **suppression of urine.** For **bacillary dysentery** 60 to 120 grs. are given three-hourly for forty-eight hours. Thereafter 60 grs. are administered four times every twenty-four hours until the stools become fæculent.

The tartrates are oxidized in the body to carbonate and render the urine alkaline. They are absorbed more easily than the sulphates and are, therefore, less purgative and more diuretic in action. The official **Potassii Tartras Acidus (B.P.) Dose, 15—60 gr. 1—4 G.** is often used for this combined mild action.

Section II

Castor Oil

Oleum Ricini (B.P.). The fixed oil expressed from the seeds of *Ricinus communis.* India.

CHARACTERS. Viscid, colourless or pale yellow. Odour faint, characteristic. Taste slight but unpleasant. *Solubility.* 1 in 1 of absolute alcohol, 1 in 3·5 of alcohol (90 per cent.).

COMPOSITION. The chief constituents are—(1) Triglyceride of ricinoleic acid. This constitutes the chief bulk. (2) Other fixed oils, as palmitin, stearin, &c.

Dose, 60—240 min. 4—16 ml.

Acidum Ricinoleicum (B.P.). A mixture of fatty acids obtained by the hydrolysis of castor oil.

CHARACTERS. Yellow, viscous liquid. *Solubility.* Free in 96 per cent. alcohol.

(Castor-oil seeds are not official. They contain 50 per cent. of the oil, and an acrid substance which makes them poisonous. Three castor-oil seeds have been known to kill an adult man. They are many times more purgative than the oil, because they contain a toxalbumin, ricin, which, when injected into the blood, is one of the most powerful vegetable poisons known. It is much less active when swallowed, as it is largely destroyed by digestive ferments. After death the mucous membrane of the intestine is violently inflamed, there are ecchymoses all over the body, and blood in the serous cavities. Ehrlich, by gradually increasing the dose of ricin, was able to render animals immune to it, and this was shown to be due to the formation in their body of antiricin, which neutralized the action of the ricin. This discovery was the basis of our knowledge of serum therapeutics.)

Action

External. Castor oil is, like olive oil, protective and sedative.

Internal. *Gastro-intestinal tract.* Medicinal doses produce no effect on the stomach. Operating chiefly on the small intestine the oil is an excellent prompt purgative, acting in about four hours, and causing little, if any, griping. As already mentioned, the purgative action is due to the formation of ricinoleic acid.

Very large doses do not cause excessive intestinal inflammation.

Therapeutics

External. Castor oil is used to protect the conjunctiva especially during chloroform and ether anæsthesia. It is soothing in conjunctivitis arising from the presence of a foreign body and may be combined with cocaine prior to its removal.

Internal. Castor oil is perhaps the best simple purgative we have. Being mild and rapid in its action it is very suitable for eliminating noxious material such as may be present in food and other forms of poisoning.

The onset of most pyrexial illnesses is accompanied by **constipation** and, in the absence of contraindication (*e.g.* appendicitis or obstruction), castor oil is the drug of choice. The headache, furred tongue and malaise are always partly relieved by its use.

It has been administered with quinine in order to induce **labour.** The oil has no direct action on the uterus, but assists the ecbolic effect of quinine by producing pelvic congestion—an accompaniment of any brisk purge.

Section III

Anthracene Purgatives

RHUBARB

Rheum (B.P.). Rhubarb Root. The rhizome of *Rheum palmatum.*

Composition. The chief constituents are—(1) *Chrysophanic acid* or *dihydroxymethylanthraquinone;* the yellow colour. (2) *Emodin or trihydroxymethylanthraquinone.* (3) *Rheotannic acid*, to which the astringency of rhubarb is due.

Dose, 3—15 gr. 0·2—1 G.

Preparations **(B.P.)**

1. **Pilula Rhei Composita.** Rhubarb, 25 ; aloes, 20 ; myrrh ; hard soap ; oil of peppermint, 2 ; syrup of glucose, 25.

Dose, 4—8 gr. 0·25—0·5 G.

2. **Pulvis Rhei Compositus.** *Synonym.* Gregory's powder. Rhubarb, 250 ; heavy magnesium carbonate, 325 ; light magnesium carbonate, 325 ; ginger, 100.

Dose, 10—60 gr. 0·6—4 G.

3. **Tinctura Rhei Composita.** Rhubarb, 100 ; cardamoms ; coriander, 12·5 ; glycerin ; alcohol (60 per cent.), to produce 1000. Percolate.

Dose, 30—60 min. 2—4 ml.

Action

External. None.

Internal. *Alimentary canal.* Rhubarb acts like any other bitter in stimulating the flow of saliva and gastric juice. In large doses it causes griping and

purgation, producing in from four to eight hours a liquid motion, coloured yellow by the chrysophanic acid. Purgation is due to the chrysophanic acid and emodin. It, like all the anthracene purgatives, is liable to gripe. The purgation is followed by constipation; this is ascribed to the tannic acid.

Kidneys. The colouring matter is excreted in the urine, and stains it yellow when acid, red when alkaline. The urinary flow is slightly increased.

Therapeutics

Rhubarb is a popular purgative in the powder form for children. It is useful in diarrhœa due to irritation caused by infected food; here the after-astringency is especially serviceable.

SENNA

Sennæ Folium (B.P.). Senna Leaf. The dried leaflets of *Cassia acutifolia* and of *Cassia angustifolia*, known in commerce as Alexandrian Senna and Tinnevelly Senna.

Composition. It contains anthracene derivatives including emodin, or trihydroxymethylanthraquinone.

Dose, 10—30 gr. 0·6—2 G.

Preparation (B.P.)

Pulvis Glycyrrhizæ Compositus. Senna leaf, 16 per cent.

Dose, 60—120 gr. 4—8 G.

Sennæ Fructus (B.P.). Senna pods. The dried ripe fruits of *Cassia acutifolia* and *Cassia angustifolia.*

Dose, 10—30 gr. 0·6—2 G.

Preparations (B.P.)

1. **Infusum Sennæ Concentratum.** Senna fruit, 80; strong tincture of ginger, 8; alcohol (20 per cent.).

Dose, 30—120 min. 2—8 ml.

2. **Infusum Sennæ.**

Dose, ½—2 fl. oz. 15—60 ml.

3. **Mistura Sennæ Composita.** *Synonym.* Black draught. Magnesium sulphate, 25; liquid extract of liquorice, 5; aromatic spirit of ammonia; compound tincture of cardamoms; infusion of senna, q.s. to make 100.

Dose, 1—2 fl. oz. 30—60 ml.

4. Syrupus Sennæ. Liquid extract of senna, 250; oil of coriander, 1·5; sugar; water to 1000.

Dose, 30—120 min. 2—8 ml.

5. Extractum Sennæ Liquidum. Senna fruit, 100; oil of coriander, 0·6; alcohol, 25; chloroform water to 100.

Dose, 10—30 min. 0·6—2 ml.

Action

External. None.

Internal. Large doses cause several evacuations and produce **griping.** Purgation by senna does not cause such constipation as does rhubarb. It will impart its purgative properties to the milk of nursing women.

Therapeutics

Senna is a safe, useful purgative for cases of simple **constipation.** The leaves, because of their tendency to gripe and nauseous taste, are rarely given alone. The compound liquorice powder is to be preferred to the black draught, as this is a nasty mixture. Acting on the colon, it is valuable in slight cases of fæcal collection. Senna forms the purgative principle of a vast array of herbal remedies and fig syrups sold under misleading names.

An infusion of senna pods is a very popular aperient, and is the least harmful purgative for regular use. It is pleasant and does not gripe, provided that the infusion be made with cold water. For an adult six may be allowed to stand in cold water for six hours and the infusion drunk the last thing at night. Sometimes more than six even up to twelve, are required at first, but the dose can nearly always be reduced by gradually using fewer pods to make the infusion.

CASCARA SAGRADA

Cascara Sagrada (B.P.). Sacred Bark. The dried bark of *Rhamnus Purshianus*, California buckthorn, collected at least one year before being used.

Composition. The chief constituents are Emodin, also contained in rhubarb and senna (*q.v.*), Cascarin, Purshianin, a glucoside, several resins, various acids, and a volatile oil.

Preparations (B.P.)

1. **Extractum Cascaræ Sagradæ Siccum.** Made by percolation with water and subsequent evaporation.

Dose, 2—8 gr. 0·12—0·5 G.

2. **Extractum Cascaræ Sagradæ Liquidum.** Made with alcohol (90 per cent.) and water.

Dose, 30—60 min. 2—4 ml.

3. **Elixir Cascaræ Sagradæ.** Cascara, 1000 ; liquorice, 125 ; light magnesium oxide, 150 ; alcohol and glycerin.

Dose, 30—60 min. 2—4 ml.

Action and Therapeutics

That of the anthracene purgatives (*q.v.*).

ALOES

Aloe (B.P.). The juice that flows from the cut leaves of various species of *Aloe* evaporated to dryness. Known as Curaçao, Socotrine, or Zanzibar aloes.

CHARACTERS. Brown, glassy masses. *Solubility.* Freely in alcohol (60 per cent.).

COMPOSITION. The chief constituents are—(1) *Aloin*, containing a methylanthraquinone derivative, barbaloin. (2) Emodin, or trioxymethylanthraquinone (see Senna).

Dose, 2—5 gr. 0·12—0·3 G.

Preparation (B.P.)

Pilula Aloes. Aloes ; hard soap ; oil of caraway ; syrup of glucose.

Dose, 4—8 gr. 0·25—0·5 G.

Aloinum (B.P.). A crystalline principle, containing barbaloin, obtained from aloes

CHARACTERS. A pale yellow microcrystalline powder, almost inodorous ; taste intensely bitter. *Solubility.* Freely in hot fluids, sparingly in cold water or cold alcohol. Decomposed by alkalies.

Dose, ¼—1 gr. 0·0015—0·06 G.

Action

External. Aloes has no external action on the unbroken skin, but it can be absorbed from a raw surface, for aloes sprinkled on an ulcer, to which it is a slight stimulant, will lead to purging.

Internal. The action is that of this group. The drawback to its use is that it is easily absorbed and may produce remote effects such as renal irritation, menorrhagia, and even abortion.

It is excreted by the milk, for aloes given to the mother may purge the child. It is also excreted in the urine.

As a rule aloin acts like aloes, but it does not gripe so much.

Therapeutics

Aloes must not be given when pregnancy, hæmorrhoids, or menorrhagia exists.

Section IV

PHENOLPHTHALEIN

Phenolphthaleinum (B.P.). $C_{20}H_{14}O_4$.

Source. Obtained by heating phenol with phthalic anhydride and sulphuric acid.

Characters. A white crystalline powder. Odourless and tasteless. Almost insoluble in water. Soluble in alcohol.

Dose, 1—5 gr. 60—300 mg.

Preparation (B.P.)

Tabellæ Phenolphthaleini. Contain 2 gr. 0·12 G. in each.

Action and Therapeutics

In susceptible persons phenolphthalein produces a widespread irritating urticarial eruption followed by staining of the skin. It may also cause toxic nephritis.

It acts with diminishing intensity for two or three days owing to partial absorption from the gut and excretion in the bile. It does not gripe, and, being tasteless, is suitable for children. It acts in about six hours, and is best given at bedtime.

Section V

SULPHUR

Sulphur is official in two forms

1. Sulphur Sublimatum (B.P.). Sublimed Sulphur. *Synonym.* Flowers of sulphur.

Source. From crude sulphur or sulphides by sublimation.

Characters. A greenish-yellow gritty powder.

Dose, 15—60 gr. 1—4 G.

Preparation (B.P.)

Unguentum Sulphuris. Sublimed sulphur, 1; hydrous ointment, 9.

2. Sulphur Præcipitatum (B.P.). Precipitated Sulphur. *Synonym.* Milk of sulphur.

SOURCE. Sulphur is precipitated by hydrochloric acid from a solution of calcium sulphides and thiosulphate.

CHARACTERS. A greyish-yellow soft powder free from grittiness.

Dose, 15—60 gr. 1—4 G.

Action of Sulphur

External. Sulphur itself has no action on the skin, but some of it is converted into sulphuretted hydrogen, and that is a mild vascular stimulant causing slight dilatation of the vessels and in some persons eczema. It kills the *Sarcoptes hominis*, and is therefore a **parasiticide.** When applied to raw surfaces it is converted into sulphurous and sulphuric acids, and is therefore a severe irritant.

Internal. *Alimentary canal.* It has no effect on the stomach, and most that is taken is passed out in the fæces unaltered. A certain amount is, in the intestine, converted into sulphuretted hydrogen and other sulphides, particularly in the colon, and these give rise to sufficient irritation to produce purgation. In therapeutic doses the effect is usually of moderate intensity, producing a soft but formed motion. Large quantities may result in violent purging. The passage of hydrogen sulphide as flatus renders the use of sulphur, over long periods, undesirable.

Remote effects. The greater part of the sulphur escapes unchanged in the fæces. About a third is absorbed as sulphides, a small proportion of which is excreted by the breath, and in the sweat, giving rise to an unpleasant odour, and blackening of silver articles carried close to the body. Most of the sulphide is converted to sulphate and excreted by the kidneys.

The intramuscular injection of sulphur is followed by the production of fever and increased tissue breakdown.

Therapeutics

External. Sulphur ointment is used in the treatment of **scabies.** The risk of dermatitis is lessened and the effective amount of sulphur reduced by using 18 per cent. sulphur soap designed to form a good lather. This is applied to the whole body and allowed to dry. A thin film of sulphur is thus deposited on the skin. Lather-producing tablets containing 0·72 gm. are still better. The procedure is repeated on two successive days. The sublimed form may be applied between the toes if affected with epidermophytosis. The lotion is valuable in the treatment of acne.

Sulphur is burnt to disinfect rooms.

Internal. Sulphur is a good **laxative,** as it produces a soft motion but no pain ; it is useful for cases of piles or fissure of the anus. Many mineral waters contain sulphides of sodium and hydrogen, the best known being found at Harrogate and Aix-les-Bains.

Remote effects. Sulphur has been administered by mouth as a treatment of various forms of chronic arthritis, but its value in this disease is doubtful. It has been employed for the production of fever in the treatment of general paralysis of the insane and of chronic, apyrexial rheumatoid arthritis. In both cases it is injected intramuscularly, usually as a 1 per cent. aqueous suspension or as a 1 per cent. suspension in oil (Sulfosin). The initial dose is ½ c.c., and injections are given on alternate days rising by ½ c.c. and closing the course at 5 c.c. The temperature rises in six to twelve hours after the injection and may reach 104° F. It is accompanied by a considerable polymorphonuclear leucocytosis.

Section VI

Drastic Purgatives

SCAMMONY

Scammonium (B.P.C.). Gum-resin from the dried root of *Convolvulus scammonia.*

Dose, 5—10 gr. 0·3—0·6 G.

Ipomœa (B.P.). *Synonyms.* Orizaba Jalap Root, Mexican Scammony Root.

Dose, 5—20 gr. 0·3—1·2 G.

Ipomœæ Resina (B.P.). *Synonym.* Scammony Resin. A mixture of resins obtained from Ipomœa.

COMPOSITION. The chief constituent is jalapin.

Dose, ½—3 gr. 0·03—0·2 G.

Action

Gastro-intestinal tract. Scammony on reaching the duodenum forms with bile a **strongly purgative** compound and produces congestion of the pelvic organs. There is little if any addition to the biliary flow. As a result, in about four hours there is a profuse **watery evacuation** of the bowels. Its action is attended with some griping. If absorbed it gives rise to cystitis and nephritis.

Therapeutics

Its chief use has been to remove fluid in dropsy and to lower intracranial pressure. In conjunction with santonin it is valuable in removing threadworms and round-worms. It should not be used in the presence of obstructive jaundice because it requires bile for its solution and action.

JALAP

Jalapa (B.P.C.). Jalap. The dried tubercles of *Ipomœa purga.*
COMPOSITION. The chief constituent is the *resin.*

Jalapa Pulverata (B.P.). Powdered Jalap. Contains 10 per cent. of resin. This is to be dispensed when jalapa is prescribed.

Dose, 5—20 gr. 0·3—1·2 G.

Preparation (B.P.C.)

Pulvis Jalapæ Compositus. Jalap; acid tartrate of potassium; ginger.

Dose, 10—60 gr. 0·6—4 G.

Action

The mode of action of jalap is precisely the **same as that of scammony,** except that it is more hydragogue.

Therapeutics

Jalap was largely used as a hydragogue purgative for patients with Bright's disease, for those suffering from uræmia, and for those with dropsy from any cause. Large doses should not be given if the intestinal mucous membrane is inflamed.

COLOCYNTH PULP

Colocynthis (B.P.). The dried pulp of the fruit of *Citrullus colocynthis,* freed from seeds.

COMPOSITION. The chief constituents are a bitter purgative alkaloid, a glucoside, and purgative resins.

Preparations (**B.P.**)

1. Extractum Colocynthidis Compositum. Colocynth; aloes; resin of scammony; curd soap; cardamoms; alcohol (60 per cent.).

Dose, 2—8 gr. 0·12—0·5 G.

2. Pilula Colocynthidis et Hyoscyami. Colocynth, 12·5; aloes, 25; scammony resin, 25; dry extract of hyoscyamus, 12·5.

Dose, 4—8 gr. 0·25—0·5 G.

Action

Its action is similar to that of jalap.

Therapeutics

Colocynth should never be given alone, because of the griping it causes. In the colocynth and hyoscyamus pill, which is often prescribed, the hyoscyamus prevents this painful result. Colocynth is an excellent purgative for producing a single abundant evacuation of the bowels. It is too irritant for habitual use. It should never be administered if there is any suspicion of intestinal or gastric inflammation, nor in pregnancy. It is often combined with milder purgatives.

PODOPHYLLUM

Podophyllum (B.P.). Podophyllum Rhizome. The dried rhizome and roots of *Podophyllum peltatum*, the American May-apple.

COMPOSITION. The chief constituents are a purgative crystalline substance *podophyllotoxin*, and the official *resin*, which is the purgative principle.

Dose, 2—10 gr. 0·12—0·6 G.

Podophylli Resina (B.P.). Podophyllum Resin.

Synonym. Podophyllin.

SOURCE. Extract the root by percolation with alcohol (90 per cent.), and precipitate the resin with water acidulated with hydrochloric acid. Wash and dry.

COMPOSITION. Podophyllum resin contains *podophyllotoxin* and *podophylloresin.*

Dose, ¼—1 gr. 15—60 mg.

Action

External. It is irritant even when applied to the skin.

Internal. Acts more slowly but not less powerfully than the other members of the group which have been described. Griping is severe.

Therapeutics

It must be remembered that, as it causes much griping, it should be combined with hyoscyamus. It is used locally in the treatment of warts, condylomata acuminata, and penile warts. A suspension of the resin, 25 per cent. in liquid paraffin, is applied for 6 hours, the surrounding skin being protected with vaseline. The emulsion is then washed off with soap and water and the parts carefully dried. It is thought advisable to use 10 per cent. in the first place because the resin is violently irritant to some people.

INDIAN PODOPHYLLUM

Podophyllum Indicum (B.P.). The dried rhizome and roots of *Podophyllum emodi.*

Dose, 2—10 gr. 0·12—0·6 G.

Action and Therapeutics

Indian podophyllum has precisely the same actions and use as the other variety.

CROTON OIL

Oleum Crotonis (B.P.C.). The fixed oil expressed from the seeds of *Croton Tiglium.*

Characters. Brownish-yellow to dark reddish-brown. Odour rancid. Taste oily, acrid. *Solubility.* Freely in alcohol or olive oil.

Composition. The active constituent is *Croton-resin* which is a powerful vesicant.

Dose, ½—1 min. 0·03—0·06 ml.—on a lump of sugar, or mixed with butter or vaseline and placed at the back of the mouth, so that it may be quickly swallowed.

Action

External. Croton oil is a vesicant and pustulant.

Internal. Very soon after a drop has been taken there is considerable griping and abdominal pain. In an hour or two the bowels are opened, and this may subsequently occur several times, the motions becoming more and more fluid. The croton oil greatly increases the vascularity of the stomach and intestines, the mucous membrane of which becomes red, œdematous, and angry-looking ; there is a great increase of the intestinal secretion, but none of the bile. The drug produces, in fact, severe **enteritis,** and to a less extent gastritis. The motions may contain blood. Croton oil applied to the skin may cause free purgation, the acid being excreted into the bowel.

Therapeutics

External. Croton oil was formerly employed externally as an irritant and counter-irritant, but is not so used now, as the scars left after the suppuration are very unsightly, and the inflammation induced too severe. A little croton oil spread over an area not exceeding that of a sixpence may be applied to set up suppuration in the scalp, and so to destroy an inveterate patch of ringworm.

Internal. Placed on the back of the tongue, it is an easily administered purgative for lunatics who refuse to take anything, and for unconscious patients, because in such cases it is swallowed reflexly and acts quickly. It must be diluted by mixture with sugar or butter to prevent local inflammation of the tongue. It should never be administered to children, to pregnant women, to feeble subjects, to those with hæmorrhoids, nor to those suffering from peritonitis, gastritis, or enteritis. Owing to its danger the drug has been almost completely discarded.

GROUP VII

Astringents

Vegetable Drugs containing Tannic Acid

The vegetable astringents which are about to be described owe their action to their precipitating proteins. This effect is due to the contained tannic acid and not to gallic acid ($C_7H_6O_5$) into which it is easily decomposed. The resulting formation of a fine pellicle of coagulated albumen over the surface of the alimentary tract reduces the absorption of toxins and protects an inflamed mucous membrane.

Internally they are used to precipitate certain poisons, *e.g.* alkaloids and salts of heavy metals, thus rendering them temporarily inert. They must, however, be removed by stomach tube and purge as promptly as possible, because the precipitate is redissolved in the intestine.

Astringents are used to check diarrhœa, the protective action diminishing the irritability of the bowel and thus checking peristalsis. The longer time which is thus allowed for absorption of fluid results in the formation of hard stools.

In irritable conditions of the colon, astringents may be used in dilute solution for bowel lavage. Repeated employment in this way produces further irritation, however.

In concentrated form, tannic acid and its congeners cause precipitation of the protein in the mucosa cells, producing severe irritation and vomiting.

The dry, rough sensation in the mouth and throat experienced when these drugs are swallowed is referable to the superficial precipitation which occurs. The same action is seen on wounds, and accounts for the value of tannic acid as a dressing for burns, and as a hæmostatic. The last effect is in no way due to action on blood vessels, but to coagulation of exudate. Intravenous injection precipitates serum proteins with the formation of emboli. Thus administered it produces collapse, convulsions, coma and death. Subcutaneous injection causes diarrhœa, wasting, pulmonary œdema and hæmorrhages into lungs and epicardium. Fatty change is produced in the myocardium and there is patchy centrolobular necrosis of the liver. The same effect on the liver may arise from absorption of tannic acid when sprayed repeatedly on extensive burns. Tannic acid and the allied acids in krameria, catechu, kino and other vegetable astringents, though precipitated in the stomach, are liberated as digestion proceeds and are thus able to exert a further action on the walls of the intestine. They do not precipitate peptones, and they are set free from protein compounds by excess acid or alkali.

The value of the crude vegetable astringents over pure tannic acid lies in the slow liberation of this substance from the gums with which it is mixed. Its unpleasant taste and irritant action are thus largely obviated.

Excretion. Tannic acid is changed to gallic acid in the intestine and so escapes in the stools, and to a less extent in the urine. This represents only a small fraction of the total acid administered, the remainder having been completely oxidized.

GALLS

Galla (B.P.C.). Excrescences on *Quercus infectoria*, caused by the puncture and deposit of the eggs of *Cynips gallæ tinctoriæ*.

COMPOSITION. The chief constituents are—(1) *Tannic acid* 60 to 75 per cent. (2) *Gallic acid*, 2 to 5 per cent.

Dose, 10—20 gr. 0·6—1·2 G.

Preparations **(B.P.C.)**

1. **Unguentum Gallæ.** Galls, 1; benzoinated lard, 4. In India benzoinated suet should be used instead of benzoinated lard.

2. **Unguentum Gallæ cum Opio.** Ointment of galls, 925; opium, 75. *Strength.*—This contains 7·5 per cent. of opium.

TANNIC ACID

Acidum Tannicum (B.P.). $C_{76}H_{52}O_{46}$. *Synonym.* Tannin.

SOURCE. Tannic acid may be extracted from galls.

CHARACTERS. A pale brownish powder, consisting of thin glistening scales. Taste strongly astringent. Reaction acid. *Solubility.* Freely in water or alcohol (90 per cent.); 1 in 1 of glycerin.

Preparations **(B.P.)**

1. **Glycerinum Acidi Tannici.** Tannic acid, 15; glycerin, 85.

Dose, 10—30 min. 0·6—2 ml.

2. **Suppositorium Acidi Tannici.** Tannic acid, 0·2 G. (3 gr.).

3. **Trochiscus Acidi Tannici.** 0·03 G. or ½ gr. in each, with a tolu basis.

Therapeutics

Excellent results have been obtained from the use of a 2½ per cent. solution for **burns.** It should not be used on the face because of cicatricial contracture which follows. The denuded area is sprayed repeatedly with the substance until it forms a pellicle. The precipitate is probably instrumental in retarding the absorption of the highly toxic products of tissue destruction, whilst it acts as an ideal protective covering to the denuded surface. Tannic acid paste is used for the same purpose and is convenient to carry during work exposing to the risk of injury by fire. The mortality from burns has been greatly reduced since the introduction of this method. As mentioned earlier the treatment is not as devoid of risk as was formerly believed. It is used as an **astringent** for ulcers, sores, various moist eruptions, tonsillitis, pharyngitis, diarrhœa, and in 1 per cent. solution as an enema for proctitis and ulcerative colitis. It is employed as a hæmostatic in bleeding from small wounds. For external use or for application to the throat the glycerinum is useful. The ointment of galls and opium is a favourite application for **piles,** but as the action of opium in relieving pain is a central one it seems pointless to apply it locally.

CATECHU

Catechu (B.P.). An extract of the leaves and young shoots of *Uncaria gambier.*

Preparation **(B.P.)**

Tinctura Catechu. Catechu, 4 ; cinnamon, 1 ; alcohol, 20. Macerate.

Dose, 30—60 min. 2—4 ml.

RHATANY

Krameria (B.P.). Krameria Root. *Synonym.* Rhatany Root. The dried root of *Krameria triandra.*

Dose, 10—30 gr. 0·6—2 G.

Preparations **(B.P.)**

1. **Extractum Krameriæ Siccum.**

Dose, 5—15 gr. 0·3—1 G.

2. **Trochiscus Krameriæ.** 0·06 G. or 1 gr. of the extract of krameria in each.

3. **Trochiscus Krameriæ et Cocainæ.** Extract of krameria, 0·06 G. ; cocaine hydrochloride, 0·003 G. ($\frac{1}{20}$ gr.).

KINO

Kino (B.P.C.). The juice obtained from the trunk of *Pterocarpus Marsupium* evaporated to dryness.

Dose, 5—20 gr. 0·3—1·2 G.

Preparations (B.P.C.)

1. Pulvis Kino Compositus. Kino, 15; opium, 1; cinnamon, 4. *Strength* of opium, 5 per cent.

Dose, 5—20 gr. 0·3—1·2 G.

2. Tinctura Kino. Kino, 10; glycerin, 15; water, 25 alcohol (90 per cent.), to make 100. Macerate.

Dose, 30—60 min. 2—4 ml.

Action and Therapeutics

The action of catechu, rhatany and kino is that of astringents, owing to their tannic acid content. They are used in preference to tannic acid for internal administration because their action will be more evenly distributed throughout the gut and they are less likely to cause irritation of the stomach. They are all incompatible with alkalies, metallic salts, and gelatin.

WITCH-HAZEL

Hamamelis (B.P.). The fresh or dried leaves of *Hamamelis virginiana.*

COMPOSITION. The leaves contain tannin. The fresh are more active than the dried.

Preparations (B.P.)

1. Extractum Hamamelidis Liquidum. Hamamelis powdered, 1000, percolated with alcohol.

2. Extractum Hamamelidis Siccum.

3. Unguentum Hamamelidis. The liquid extract, wool fat and yellow soft paraffin.

4. Suppositoria Hamamelidis. Dry extract, 3 gr. 0·2 G.

5. Suppositoria Hamamelidis et Zinci Oxidi. 3 gr. and 10 gr. respectively.

Therapeutics

This is a useful astringent, particularly for application to the eye, skin and anal canal. It is much less irritant than other members of the group.

GROUP VIII

Cholagogues

Bile

Drugs which increase the amount of bile actually secreted are called **direct cholagogues,** of which bile and bile salts only are effective: those which simply lead to a larger amount of bile being found in the fæces without any extra secretion have been termed **indirect cholagogues,** but the term is falling into disuse. These cause no increase in the amount of bile secreted; they act either by stimulating the upper part of the jejunum and the lower part of the duodenum, thus sweeping the bile on before there is time for it to be reabsorbed; or because the purgative, *e.g.* jalap, or scammony, acts best on the intestine when dissolved in bile, and hence when there is plenty of bile in the intestine it is quickly expelled; or because the drug promotes evacuation of the gall-bladder, *e.g.* magnesium sulphate.

Indirect cholagogue action is of value in chronic infection of the gall-bladder and bile ducts because it promotes drainage. It is quite possible that this stimulates further secretion, in which case the distinction between direct and indirect cholagogues cannot be maintained.

OX GALL

Extractum Fellis Bovini (B.P.). Purified Ox Bile. The purified gall of the ox.

CHARACTERS. Yellowish-green. Soluble in water and in alcohol.

Dose, 5—15 gr. 0·3—1 G.

Action

Bile increases the activity of the pancreatic lipolytic ferment and aids the absorption of fats. It has a mild laxative action due to irritation of the colonic mucosa by the bile acids. It appears also to retard putrefactive processes in the bowel.

Most of the bile administered per os is absorbed from the intestine and re-excreted by the liver. The resultant output of bile is so great that it is clear that the substance acts as a true cholagogue. This effect is referable to stimulation of the secretory cells of the liver by the bile acids.

Bile salts when injected into the blood depress the central nervous system and the heart muscle and dissolve the red cells. The slow pulse of jaundice is referable to direct action on the myocardium.

Therapeutics

Bile may be used to aid the absorption of fats as in cases of biliary fistula.

Cholagogue action is seldom indicated, but bile has been advocated for use in the later stages of catarrhal jaundice when a mild residual icterus persists. It is often administered as Felamine which is hexamine glycocholate in tablets of 0·3 grm. As a mild purgative bile is of undoubted value and has also been employed in the form of an enema (2 oz. bile (human if obtainable) in 4 oz. saline 4-hourly), particularly in cases of **ileus.**

Migraine appears in certain persons to be associated with, and possibly due to, derangement of hepatic function. In such cases the administration of cholagogues has been of value in preventing and aborting attacks. The best-known preparation for this purpose is Decholin (**dehydrocholic acid**), two tablets of 0·25 grm. each being given twice or thrice daily. The dose must be reduced if diarrhœa begins. The increased bile flow is evidenced by the colour of the stools.

To determine the rate of circulation of the blood, 10 mils of 20 per cent. solution of **Sodium dehydrocholate** are injected quickly intravenously. The time taken from the injection to the appearance of a bitter taste in the mouth is taken as that of the complete circuit. The normal circulation time is 10 to 17 secs. ; in heart failure, 23 to 40 secs. The test does not distinguish between right and left ventricular failure. To do this 5 minims of ether may be injected to record the arm-to-lung time. This figure (normal 4–8 secs.) subtracted from the Sodium dehydrocholate reading gives the pulmonary circulation time (normal 4·5–10 secs.).

GROUP IX

Anthelmintics

Anthelmintics are drugs which are used to remove or kill intestinal worms. In many cases the parasites are not killed in the gut, but are so violently stimulated or stupefied by the drug that they are swept away by the subsequently administered purge.

CLASS I. *Anthelmintics* for the various species of *Tapeworm.*
Male Fern, Pelletierine Tannate, Cusso.

CLASS II. *Anthelmintics* for the *Roundworm* (*Ascaris lumbricoides*).
Santonin, Oil of Chenopodium (also Class III).

CLASS III. *Anthelmintics* for *Hookworms* (*Ankylostoma duodenale and Necator americanus*).
Thymol, Carbon Tetrachloride, Tetrachlorethylene, Oil of Chenopodium, B-naphthol (*see Antiseptics*).
CLASS IV. *Anthelmintics* for the *Threadworm* (*Oxyuris vermicularis*).
Quassia (*see Bitters*), **Carbon Tetrachloride** (also Class III), **Diphenan, Phenothiazine, Gentian Violet** (*see Antiseptics*).

CLASS I. Anthelmintics used for Tapeworms

MALE FERN

Filix Mas (B.P.). Male Fern. The rhizome of *Dryopteris Filix-mas.*
COMPOSITION. The chief constituents are—(1) *Filicin* (Filicic acid), the active principle. (2) Resins.

Preparation **(B.P.)**

Extractum Filicis. *Synonym.* Liquid extract of male fern. Male fern is percolated with ether, which is then evaporated, and an oily liquid is left, which is really an oleoresin.

Must contain 25 per cent. of filicin in 100 grms. of the liquid extract.

Dose, 45—90 min. 3—6 ml.—in an emulsion with mucilage of acacia or tragacanth, or with milk, as water precipitates the resin.

Action

The extract kills or dislodges tapeworms.

Toxic doses are severe gastro-intestinal irritants, and also cause muscular weakness, coma, and optic neuritis. Slight jaundice may supervene and is of hæmolytic origin. The drug is cumulative.

Therapeutics

Male fern is an **anthelmintic** for **tapeworms.** After a twelve-hour fast the intestine is emptied with a saline purge to ensure the worm's not being protected by food, the male fern should be administered, and in three hours another dose of the purgative should be given to clear away the worm. Castor oil must not be used because oils aid the absorption of filicic acid which is toxic. No food should be taken during the treatment. The head of the worm should be carefully searched for in the motion. In case of failure, a week should elapse before repetition of treatment on account of the cumulative action.

PELLETIERINE TANNATE

Pelletierinæ Tannas (B.P.). A mixture of the tannates of the four alkaloids pelletierine, isopelletierine, methylpelletierine and pseudopelletierine obtained from pomegranate bark.

Characters. A light yellow amorphous powder, slightly soluble in water, more in alcohol.

Dose, 2—8 gr. 0·12—0·5 G.

Action

The drug has a specific action on tapeworms, which are killed in ten minutes by a dilution of 1 in 10,000. As the contents of the small intestine during fasting are about 200 c.c., the maximum dose of pelletierine will produce the highly efficacious concentration of 25 in 10,000.

The tannate is three times as effective as the sulphate because it is slowly dissolved in the intestine and absorption is slight.

Muscular weakness, nausea, vomiting, diarrhœa and blurred vision occasionally result from its action during and after absorption.

Therapeutics

The usual precautions of purgation and preliminary starvation must be observed. The requisite dose may be administered in aqueous suspension; being very insoluble, it passes unchanged in the stomach, and by the time it reaches the intestine enough of it is dissolved to kill the tapeworm. It should be followed after two hours by a purge.

CUSSO

Cusso (B.P.C.). The dried panicles of pistillate flowers of *Brayera anthelmintica.* Abyssinia.

COMPOSITION. The chief constituent Koussin, or Koussotoxin, a neutral active principle soluble in alkalies.

Dose, 120—240 gr. 8—10 G.

Action and Therapeutics

Cusso is rarely given in England, but is used abroad as an **anthelmintic** for all species of tapeworm. It is best given as an unstrained infusion. A purgative is seldom required after using cusso.

CLASS II. Anthelmintics used for Roundworm

SANTONIN

Santoninum (B.P.). Santonin, $C_{15}H_{18}O_3$. A neutral crystalline principle obtained from *Artemisia pauciflora.*

CHARACTERS. Colourless prisms, turning yellow on exposure to light. Tasteless or feebly bitter. *Solubility.* Feebly in cold water, easily in chloroform. It forms santonates with alkalies.

Dose, 1—3 gr. 60—200 mg.

Action

The drug stimulates the roundworm and in this way helps to dislodge it from the small intestine into the large gut whence it is expelled alive by a purge. Dissolved in bile, santonin is more toxic to *Ascaris.* This fact is of importance because it has been shown that the drug is absorbed extensively from the duodenum and is carried to the liver, to be partly re-excreted in the bile. Medicinal doses will usually cause the urine, if it is acid, to be a saffron colour, and if it is alkaline to be purplish red. This is due to the excretion in that fluid of some substance resulting from the changes undergone by santonin in the body. Excretion takes two to three days to be complete, and is largely in the urine. Often even small doses lead to xanthopsy (yellow vision). Sometimes this is preceded and followed by violet vision. It is due to stimulation followed by depression of the violet-perceiving mechanism of the retina.

Several cases of fatal poisoning by santonin are on record. Cerebral symptoms are very prominent. Thus convulsions, accompanied by unconsciousness, trismus, and dilated pupils, are generally present. The surface becomes cold, there is sweating, there may be trembling, the pulse and respiration become weaker and weaker, and death takes place from cardiac and respiratory failure.

Therapeutics

Santonin is used especially in the treatment for roundworm. It is of some value for thread-worm. The dose of it should be given at bed-time after a day's light diet. Calomel may be given at the same time. A saline cathartic should be given on the following morning. The first dose should not exceed 3 grains for an adult or 1 grain for a child, in view of the real danger of idiosyncrasy. Four days should elapse before repeating treatment. Preliminary purgation and starvation are to be avoided because they increase the risk of absorption (*see also* Thymol).

Class III. Anthelmintics used for Hookworm

THYMOL

Thymol (B.P.). $C_{10}H_{14}O$. A crystalline substance obtained from the volatile oils of *Thymus vulgaris*, *Monarda punctata*, and *Carum copticum*.

Characters. Prismatic crystals. Odour of thyme. *Solubility*. 1 in 1500 of cold water, 1 in 2 of olive oil. Freely in alcohol, ether, or chloroform.

Dose, ½—2 gr. 30—120 mg.; 15—30 gr. 1—2 G. (anthelmintic).

Action

Thymol is a more powerful **antiseptic** than carbolic acid, but its insolubility greatly limits its use in this respect. It is less toxic than phenol.

Administered by mouth it is completely absorbed, and 75 per cent. is destroyed in the tissues. The remainder is excreted in the urine, the process starting in one hour and being complete in twenty-four hours.

Large doses irritate the mucosa of stomach and small intestine and, after absorption, produce tinnitus, vomiting, headache, renal irritation, and collapse.

Therapeutics

Thymol is a useful anthelmintic for the hookworms, *Necator americanus* and *Ankylostoma duodenale*, but kills only some 70 per cent. of the worms whereas the other drugs used for this purpose attain a figure of 90 per cent. or more. It has, also, a slight anthelmintic action against roundworm.

After twelve hours' starvation and the use of a purge, the drug is administered in cachet form or powder mixed with sugar in a dose of 30 grains (2 grms.). This is repeated in two hours and a saline purge given two hours later. No food may be taken until this has acted. Repeat in five days if necessary.

CARBON TETRACHLORIDE

Carbonei Tetrachloridum (B.P.). (CCl_4). Tetrachlormethane. A colourless liquid with odour of chloroform. Non-inflammable. Slowly decomposed by light. *Solubility.* 1 in 2000 of water: freely in alcohol, chloroform and volatile oils.

Dose, 30—60 min. 2—4 ml. Not to be repeated within three weeks. For children: 2 minims for each year of age up to puberty.

Action

External. No effect on skin, but produces a sensation of heat if applied to mucous membranes. Hypodermic injection may result in necrosis.

Internal. Carbon tetrachloride acts more powerfully on *Necator americanus* than upon the more dangerous *Ankylostoma duodenale.* It is superior in effect to oil of chenopodium, but more liable to produce toxic effects. It has the advantage of being relatively cheap. Absorption is rapid from all mucous membranes, and the greater part is eliminated in the expired air. The systemic action is similar to that of chloroform, depression of the higher centres of the nervous system producing drowsiness and even narcosis. Some such result may follow the ingestion of 5 c.c. Central fatty degeneration of the liver and scattered hæmorrhages, nephrosis and uræmia, may also be observed after a single dose.

Fatalities have occurred after therapeutic doses, and are due to the effect on the liver. This depends upon individual idiosyncrasy, or upon partial obstruction of the gut by food or worms, or upon chronic alcoholism, or upon a deficiency of calcium in the blood. The baneful effect of alcohol is due to synergistic action on the liver, and not to its aiding absorption. The administration intravenously of calcium chloride or the intramuscular injection of parathormone, will favourably influence the course of tetrachloride poisoning. If the drug is impure it is extremely toxic.

Therapeutics

Carbon tetrachloride is used for the treatment of hookworm infestation. It must not be given to alcoholics. The likelihood of liver damage can be reduced by the administration of an ounce of glucose twice daily for two days before commencing treatment. The toxic effects on the nervous system can be prevented by an intramuscular injection of 10 minims of parathormone daily for two days and administration of calcium gluconate. The drug is then given shaken up in milk. Preliminary starvation and purgation must be avoided. It has a slight purgative action, but it is well to give a saline cathartic three hours after administration.

It is of use in threadworm infestation, and is given by mouth and *per rectum* (6 c.c. in milk as an emulsion).

TETRACHLORETHYLENE

Tetrachlorethylenum (B.P.). C_2Cl_4. Colourless heavy liquid. Odour similar to carbon tetrachloride. Insoluble in water; miscible with alcohol and oils.

Dose, 15—45 min. 1—3 ml.

Action

Similar to that of carbon tetrachloride but is absorbed less readily. Its toxicity is thus lower; a fact which has led to rapid extension of its use. Doses of 4 mils have been known to cause deep coma, loss of reflexes, and contracted pupils. The pulse is strong. Recovery occurs in a few hours and is accelerated by the injection of nikethamide.

Therapeutics

Tetrachlorethylene is the drug of choice in the treatment of hookworm infestation. It is usual to administer a 1 mil capsule hourly for four to five hours on two successive days and to follow the last dose in three hours' time with a saline purge. Alternatively a single dose of 60 minims, with 15 minims of chenopodium oil and 2 oz. of saturated magnesium sulphate, may be given as an emulsion.

CHENOPODIUM

Oleum Chenopodii (B.P.). *Synonym.* American Wormseed Oil.

SOURCE. Distilled from the fresh plant *Chenopodium ambrosiodes.*

CHARACTERS. A volatile oil; pale yellow; bitter taste. It should contain at least 65 per cent. of Ascaridole ($C_{10}H_{16}O_2$). *Solubility.* 1 in 8 of 70 per cent. alcohol.

Dose, 3—15 min. 0·2—1 ml.

Action

The efficacy of the oil is due to ascaridole.

External. Slightly irritates the skin; similar but more pronounced effect on mucous membranes.

Internal. The drug produces a feeling of warmth in the mouth and stomach, and excites salivation. It is absorbed rapidly from the duodenum and excreted chiefly through the lungs; partly by the kidneys. It is active against hookworm and ascaris, and is more effective than santonin against the latter. It seldom gives rise to poisoning. It has some action against threadworm. The systemic action is characterized by depression of the central nervous system with giddiness, vomiting, coma, and death due to paralysis of the respiratory centre. Tinnitus and temporary or permanent deafness may follow its use.

Therapeutics

Oil of chenopodium is used extensively against *Ankylostoma duodenale.* It is less effective than carbon tetrachloride against *Necator.* Preliminary purgation and starvation must be avoided. In the morning 30 minims of the oil mixed with sugar are given hourly for three doses. Two hours after the last dose magnesium sulphate should be taken. Probably the most efficient treatment is the combination of oil of chenopodium (15 minims), tetrachlorethylene (60 minims), and saturated magnesium sulphate (2 ozs.) given as a single dose. To children 2 minims of oil of chenopodium for each year of age is given on sugar.

Against *Ascaris* the dose is smaller, *e.g.* 5 to 10 minims thrice daily for two days followed by a purge.

CLASS IV. Anthelmintics used for Threadworm

DIPHENAN

Diphenanum (B.P.). *Tr. Names.* Oxylan ; Butolan. It is p-benzyl-phenyl carbamate.

Dose, 8—15 gr. 0·5—1 G. For adults 0·5 G. is given thrice daily for a week. The dose should be halved for children below ten years of age.

Action

A 1 in 4000 solution kills oxyuris in five minutes. It probably kills the young parasites in the intestine. The drug is singularly free from toxic effects, but may cause diarrhœa. It is wise to wash out the colon with quassia infusion daily ; to administer dilute hydrochloric acid by mouth and to smear the perianal skin with a weak mercury ointment.

PHENOTHIAZINE

Characters. A lemon-yellow powder; taste bitter. Insoluble in water.

Maximum dose, 90 gr. 6 G. daily for seven days—for an adult man.
75 gr. 5 G. daily for seven days—for an adult woman.
30 gr. 2 G. daily for seven days—for children under eight.
15 gr. 1 G. daily for seven days—for children under four.

Action

Phenothiazine destroys threadworm and helps to dislodge round-worm. Some is absorbed from the gut and may produce **toxic hepatitis** and severe **anæmia.** This is especially liable to occur in children. It is oxidized in the body and excreted in the urine, which may become red owing to oxidation to a dye. It is a **urinary antiseptic.**

Therapeutics

Its chief value is in the treatment of infestation with *Oxyuris vermicularis.* It is unnecessary to restrict food intake or to give purges. **The danger of poisoning must be borne in mind.** It is probably less effective than gentian violet.

(*See also* Quassia, Carbon Tetrachloride, Oil of Chenopodium, Santonin, Methylene Blue *and* Gentian Violet.)

GROUP X

Antiseptics

An antiseptic is a substance which is used to inhibit the growth of micro-organisms, whereas a disinfectant is a drug used to kill them. It will be clear from considerations which follow that substances do not fall naturally into one or other class, for a drug which in certain circumstances is disinfectant will, in other circumstances, act only as an antiseptic.

The activity of a disinfectant is usually measured by the Rideal-Walker test. The essential point of the method is that its action is compared with that of phenol on microbes under precisely similar conditions. The information thus obtained is only of limited value because the efficiency of an antiseptic in relation to phenol may be profoundly modified by certain factors, of which the following are the chief: (1) Temperature.

A rise enhances the action but in varying degrees, *e.g.* much more for phenol than for mercury perchloride. (2) Length of time in contact with microbes. Colloidal metals are efficient antiseptics if allowed to act for several hours, but useless if applied for a few minutes. (3) The number of microbes present, and the amount of organic matter in the surrounding medium. As a rule the activity of a disinfectant varies inversely with the number of microbes. Again, many drugs, though powerfully disinfectant in a watery medium, lose potency almost entirely if in contact with organic matter. Mercury perchloride and cresol are thus rapidly deprived of efficiency, and are consequently of but little value for use on the human body in ordinary pyogenic infections. Phenol is less affected, whilst acriflavine actually acts more powerfully in serum than in water. (4) Species of bacteria. For instance, coal-tar products are much more effective against *B. pestis* than *Staphylococcus aureus.* (5) The medium in which the disinfectant is dissolved. If the drug is more soluble in the vehicle than in the protoplasm of the organism it will not leave the former for the latter. Thus the activity of carbolic acid is enormously reduced by solution in alcohol or oil owing to this influence of differential solubility. The salts of the heavy metals lose potency if dissolved in strong alcohol, but this is due to imperfect dissociation in that medium : the effect is reversed if weak alcohol is employed. (6) The degree of concentration of the drug. In most cases the higher the concentration the more rapid the disinfectant action, but the parallelism falls off as one approaches the high figures. Alcohol shows this in striking degree for absolute alcohol has only a fraction of the disinfectant power of a 60 per cent. solution.

The use of disinfectants on the human body is greatly hampered by the fact that these drugs are protoplasmic poisons and, in general, exert as harmful an effect on the tissues of the host as on the invading organisms ; they lack, in fact, specific affinity for the microbes such as is possessed by certain drugs for organisms of the animal kingdom. Therapeutically, the value of this series lies, therefore, almost solely in antiseptic as opposed to disinfectant action. The injection of various disinfectants into the blood stream has been lauded from time to time for the treatment of septicæmic states. In point of fact, the fall of temperature which may follow is only evidence of poisoning by the drug, the patient's general condition showing no corresponding amelioration.

The introduction of the **Sulphonamides** marked a new era of chemotherapy in that, for the first time, a drug was discovered which would lead to the destruction of microbes widely disseminated throughout the body. They are not *Antiseptics* and are described in a subsequent chapter.

Finally **Penicillin** (*q.v.*) provides the first instance of a powerful bacteriostatic which has no toxic effect on the host.

Metallic disinfectants, balsams, and the cubebs group of genito-urinary antiseptics have been omitted from the following section as they are discussed under their appropriate headings.

CARBOLIC ACID

Phenol (B.P.). Phenyl alcohol. C_6H_5OH.

Source. From coal-tar oil by fractional distillation, and purification.

Characters. Colourless deliquescent crystals. Often reddish from impurities, which form a red compound by the absorption of CO_2 and oxygen. Melts at 40° C. to an oily liquid. Faintly acid to litmus paper. *Solubility.* 1 in 13 of water; freely in alcohol, fats, and oils.

Preparations (B.P.)

1. **Phenol Liquefactum.** Phenol, 8; water, to produce 10.
2. **Glycerinum Phenolis.** Phenol, 160; glycerin, 840.

Dose, 5—15 min. 0·3—1 ml.

Dilution with water renders it caustic. Glycerin should be used.

3. **Suppositorium Phenolis.** 1 gr. (0·06 G.) in each.
4. **Trochiscus Phenolis.** Phenol, 35·5; refined sugar; acacia, 90; tragacanth, 30; citric acid, 7.

Each lozenge contains 0·03 G. of Phenol or approximately ½ gr.

5. **Unguentum Phenolis.** Phenol, 3 per cent. paraffin, lard, and beeswax.

Action

External. Carbolic acid, being a protoplasmic poison, is a powerful **antizymotic,** rapidly destroying organized ferments, both animal and vegetable. It is **antiseptic, disinfectant,** and **deodorant.** Its action on micro-organisms is largely due to its being more soluble in lipoids and proteins than in water. Consequently it leaves watery media and concentrates in the microbial bodies. The importance of this differential solubility must be borne in mind, for oily preparations are valueless as antiseptics. On the other hand, the addition of sodium chloride reduces the solubility of phenol in water and renders it a more efficient disinfectant. It does not act so readily on unorganized ferments (enzymes), such as pepsin and ptyalin, but in large doses it likewise destroys their activity. Carbolic acid has the great practical advantage that its efficacy is not much reduced by the presence of organic matter.

When applied to the skin in weak or moderately strong solutions, it produces **local anæsthesia** with a feeling of numbness, which lasts some hours. If concentrated it acts as an **irritant** and **caustic,** causing a burning pain, and in a few minutes a white spot appears, which becomes red when the acid is removed. If the application is prolonged a white eschar or slough results. There is no vesication. The local action is due to the precipitation of proteins, but carbolic acid is not firmly held in the precipitate and is thus able to penetrate considerably further than the metallic antiseptics.

Carbolic acid is absorbed from the skin, mucous membranes, and raw surfaces, and poisoning has often occurred as a result of the prolonged use of phenol dressings.

Internal. *Gastro-intestinal tract.* If concentrated, phenol produces the same effect on the mouth as on the skin, and is a powerful gastro-intestinal irritant. In the stomach it is converted into a sulphocarbolate, and unless poisonous doses be given, it is so diluted by the gastric contents that it loses its antizymotic power.

Blood. Phenol causes clotting of blood if given as intravenous injection.

Circulation. Medicinal doses have no effect. Large doses paralyse the vaso-motor centre in the medulla, and the blood pressure falls. It is not until very large doses have been given that the heart is affected, and then its activity is depressed.

Respiration. Small doses have no influence on respiration, but large ones accelerate it, probably from stimulation of the respiratory centre which is ultimately paralysed.

Temperature. This is unaffected by small doses of carbolic acid, but large doses cause it to fall.

Nervous system. Carbolic acid is a cerebral depressant in large doses, for coma is produced by them ; they first stimulate the anterior cornua and cortex, producing convulsions in animals, but rarely in man. This is followed by depression and paralysis.

Urine. Even after moderate doses of carbolic acid, or absorption from surgical dressings, **the urine may become dark,** especially on being kept exposed to air. After taking carbolic acid, salts of phenol sulphuric acid and glycuronic acid, pyrocatechin and hydroquinone appear in the urine. The last two are oxidation products of carbolic acid, which on further oxidation produce dark-coloured substances, which are the cause of the colour of the urine. When very large doses are given, carbolic acid itself may appear in the urine in the free state.

Therapeutics

External. Carbolic acid is largely used as a deodorant and disinfectant for drains, bed-pans (for which the cheap crude acid may be employed), soiled linen, surgical instruments, the surgeon's hands, &c. Its use on wounds is unwise on account of the danger of absorption. Prolonged local application, under dressings, to the fingers has been known to produce gangrene. For itching skin affections, especially if the epidermis is intact, it may be used as a 1 per cent. lotion on account of its local anæsthetic properties.

Glycerin of carbolic acid is used for infections of the external auditory meatus and in otitis media. On no account should it be diluted with water.

Internal. The drug is no longer given internally.

Toxicology

If carbolic acid is at all concentrated, immediately on swallowing it there is an intense burning sensation in the mouth, gullet, and stomach, and white eschars form in the mouth. The patient is collapsed, his skin is cold and clammy. The breathing becomes more and more feeble and shallow, and finally stops. The urine is darkish green. Reflex movements are abolished, and ultimately he becomes insensible and comatose. The pupils are contracted. *Post-mortem.* There are white, hard sloughs, with perhaps inflammatory redness round them, in the mouth, œsophagus, and stomach. The blood is dark and coagulates imperfectly. In some cases fatty degeneration of the liver and kidneys may be found. Smaller doses produce acute nephritis.

Treatment. Stomach tube and thorough lavage with 10 per cent. alcohol: the acid is more soluble in this than the gastric juices. Apomorphine is a suitable emetic. Use radiant heat cradle, strychnine and caffeine for collapse.

SALOL

Salol (B.P.C.). Phenyl salicylate. $C_{13}H_{10}O_3$.

SOURCE. Prepared by the interaction of salicylic acid and phenol.

CHARACTERS. Small colourless crystals of a faint aromatic odour and almost tasteless. *Solubility.* 1 in 15 in alcohol (90 per cent.), 3 in 1 in ether or chloroform. Contains 60 parts of salicylic and 40 of carbolic acids.

Dose, 5—20 gr. 0·3—1·2 G.

Action and Therapeutics

EXTERNAL. None.

INTERNAL. In the intestine salol is split by pancreatic lipase into carbolic and salicylic acids, and the former may render the urine dark. Large doses may give rise to typical carbolic acid poisoning.

It has been used as an intestinal disinfectant, but its value is doubtful. It acts as a mild disinfectant of the urinary tract by virtue of the absorbed carbolic acid.

CRESOL

Cresol (B.P.). A mixture of three isomers, meta-, ortho- and paracresol, of the formula C_7H_7OH obtained from coal tar.

CHARACTERS. A straw-coloured liquid, becoming brown on keeping or on exposure to light. Soluble in 50 parts of water.

Preparation (B.P.)

Liquor Cresolis Saponatus. *Synonym.* Lysol.

Source. A mixture of cresol, linseed oil, potassium hydroxide, distilled water.

Chlorocresol (B.P.). *Synonym.* Parachlorometacresol. *Solubility.* 1 in 250 of water.

Action

Cresol is a more powerful antiseptic than carbolic acid when tested in water, but the addition of fæces to make an emulsion of 3 per cent. reduces the activity to only slightly above that of phenol. The cresols are used as soapy emulsions and are actively bactericidal in concentration. A third is excreted in the urine as cresyl-sulphonic and glycuronic acid. The rest is oxidized.

Halogenated derivatives of phenol and cresol have greatly increased disinfectant action. Thus chlorocresol is at least five times more powerful than phenol in antiseptic action and its toxicity is relatively low. The highly popular **Dettol** is a complex synthetic antiseptic of this group. It is far less irritating to the tissues than cresol and much more powerful in disinfectant action.

Therapeutics

Cresol is used in surgery and generally as an antiseptic, and may with advantage replace carbolic acid for disinfection of instruments and rooms. It is rarely used on the human body because of the loss of activity in the presence of organic matter. It has a reputation for use in whooping-cough if volatilized in the sick room. Chlorocresol is much used as a preservative of solutions of drugs for hypodermic injection.

Toxicology

Cresol and its allies being so common have led to many cases of poisoning. The symptoms are like those of carbolic acid poisoning, but absorption does not occur so readily as in the case of phenol. The stomach should be immediately washed out and then white of egg or olive oil should be given to prevent the absorption of any of the poison from the stomach.

CHLOROXYLENOL

Chloroxylenol (B.P.). *Synonym.* Parachlormetaxylenol.

Preparation **(B.P.)**

Liquor Chloroxylenolis. *Synonym.* Roxenol. Consists of 5 per cent. chloroxylenol with terpineol and ricinoleic acid in distilled water.

Action

A non-irritant antiseptic of low toxicity. Owing to low solubility in water it must be used in alkaline or soapy solutions. The liquor is used for **wounds** (ʒi to ⊙i) and as a **vaginal douche** (ʒiii to ⊙i).

BETANAPHTHOL

Betanaphthol (B.P.). $C_{10}H_7OH$. *Synonym.* Naphthol.

Source. Prepared from naphthalene-sulphonic acid.

Characters and Tests. White crystals or powder. Odour like phenol; taste pungent. *Solubility.* Easily in alcohol, ether, chloroform, 1 in 8 of olive oil.

Dose, 5—10 gr. 0·3—0·6 G.

Action

Its antiseptic action is similar to that of phenol, but more powerful. It is irritating to mucous surfaces and to the urinary tract in the course of excretion in combination with glycuronic and sulphuric acid. Large doses produce symptoms similar to those of phenol poisoning. Retinal degeneration and optic atrophy may follow prolonged administration.

Therapeutics

As a 10 per cent. ointment it has been used for **scabies** and ringworm. It was extensively employed in the treatment of **hookworm** disease until superseded by carbon tetrachloride and oil of chenopodium.

Scarlet Red (B.P.C.). A derivative of naphthol. A red powder soluble in oils and fats. An excellent stimulating ointment (4 to 8 per cent. with a lard basis). The dressing should be changed night and morning.

Naphthalenum (B.P.C.). $C_{10}H_8$. *Synonym.* Naphthalin, Tar Camphor.

Dose, 3—12 gr. 0·2—0·8 G.—in a cachet.

It is an antiseptic and is much used instead of camphor to prevent the ravages of moth in furs.

TAR

Pix Liquida (B.P.). Wood Tar. A bituminous liquid obtained from the wood of *Pinus sylvestris.*

Characters. *Solubility.* 1 in 10 of alcohol (90 per cent.), slightly in oil of turpentine or olive oil, 1 in 3 of a solution of caustic soda. On distillation it gives off oil of tar. What remains behind is pitch.

Composition. The chief constituents are—(1) Oil of turpentine. (2) Creosote. (3) Phenols. (4) Pyrocatechin. (5) Acetic acid. (6) Acetone. (7) Xylol. (8) Toluol. (9) Methylic alcohol. (10) Resins.

Preparation

Unguentum Picis Liquidæ. Wood tar; prepared lard; yellow beeswax.

In India prepared suet should be used instead of prepared lard.

Pix Carbonis Præparata (B.P.). Prepared coal tar.

Source. Commercial coal tar is stirred and heated at 50° C. for 1 hour.

Characters. A nearly black, viscous liquid, heavier than water. Soluble in benzene and chloroform, very slightly in water.

Composition. It contains chiefly—(1) Benzene and homologous hydrocarbons. (2) Phenols. (3) Solid hydrocarbons, as naphthalene and anthracene.

Preparation (B.P.)

Liquor Picis Carbonis. Quillaia; alcohol (90 per cent.); prepared coal tar (20 per cent.).

Action

External. Tar has considerable antiseptic properties, and is mildly rubefacient.

Internal. It is very liable to upset digestion; in large doses it causes epigastric pain, vomiting, severe headache, dark urine, and other symptoms of carbolic acid poisoning. Some of its constituents are excreted by mucous membranes, especially the bronchial, on which it acts as a mildly antiseptic expectorant.

Therapeutics

External. Tar ointment, which is rather hard, and may be softened by replacing half the wax with almond oil, is often applied as a stimulant to chronic skin diseases, such as psoriasis and chronic eczema. Because of its mildly local anæsthetic action, it is sometimes useful in pruritus.

Liquor Picis Carbonis is a favourite preparation for many skin diseases.

Internal. Coal tar is rarely prescribed for internal use. Wood tar is only given as an expectorant for chronic bronchitis. It may be prescribed as the Syrupus Picis Liquidæ (**B.P.C.**, dose 1 to 2 fl. dr.—4 to 8 mils).

CREOSOTE

Creosotum (B.P.). Source. Obtained by the distillation of wood tar, by which the more poisonous phenols are removed. It consists of a mixture of guaiacol ($C_7H_8O_2$), creosol ($C_8H_{10}O_2$), and of other phenols.

Characters. A colourless or slightly yellow liquid, with a smoky odour and a burning taste. *Solubility.* 1 in 150 in water, freely in alcohol, ether, and glacial acetic acid.

Incompatible. Explodes when mixed with oxide of silver.

Dose, 2—10 min. 0·12—0·6 ml.

Preparation (B.P.C.)

Unguentum Creosoti. Creosote, 1; hard paraffin, 4; white soft paraffin, 5.

Action and Therapeutics

Creosote has the same actions as carbolic acid, but is less likely to produce nervous symptoms and is less toxic. Only small amounts are excreted through the bronchial mucous membrane, most being passed out in the urine in combination with sulphuric and glycuronic acids. It was at one time used extensively by internal administration in the treatment of pulmonary tuberculosis, the drug being given in capsules up to 4 mils daily. It has no specific effect upon the disease, however, and frequently causes heart-burn and nauseous eructation. On the other hand, it is of value as a deodorant and possibly as an antiseptic if inhaled in a state of fine division in cases of bronchiectasis and of pulmonary abscess.

BENZENE

Benzenum (B.P.C.). A mixture of homologous hydrocarbons obtained from light coal-tar oil. It contains about 70 per cent. of benzene, C_6H_6, and 20 to 30 per cent. toluene, C_6H_5, CH_3.

CHARACTERS. A colourless volatile liquid with strong characteristic odour.

Dose, 5—10 min. 0·3—0·6 ml.

Action and Therapeutics

One free application will destroy pediculi capitis and pediculi pubis. It causes a marked fall in the number of leucocytes in the blood, and has thus been used for leukæmia. For this purpose 40 to 60 ♏ (24 to 36 decimils) have been given in capsules. The treatment is distinctly dangerous and uncertain. It has been superseded by the use of deep X-rays.

ACRIFLAVINE

Acriflavina (B.P.). A coal-tar product, formerly called Flavine. A brick-red powder, used in aqueous solution of 1 in 1000. Precipitates with saline if not freshly prepared.

Dose, ½—1½ gr. 0·03—0·1 G.

Proflavinæ Hemisulphas (B.P.). *Synonyms.* Neutral Proflavine Sulphate; Proflavine. A red, crystalline powder, soluble in 150 parts of water.

Very powerful antiseptic, acts in the presence of organic matter, stimulates connective tissue cells, does not destroy leucocytes and is therapeutically perhaps the best antiseptic. Its disinfectant action as tested against the *Staphylococcus aureus* is greatly enhanced by the presence of serum. In this respect the drug is unique. Proflavine has the same action and is less toxic.

AMINACRINE

Aminacrinæ Hydrochloridum (B.P.). Aminoacridine hydrochloride monohydrate. Yellow, odourless powder, soluble in 300 parts of water; freely in alcohol.

Action

An antiseptic of neutral reaction. It does not stain.

Viride Nitens (B.P.). Brilliant Green. A coal-tar product. Very powerful antiseptic, used to promote granulation of wounds (1 in 1000 aqueous sol.). Equal parts of brilliant green and crystal violet in 1 per cent. solution form an efficient disinfectant for painting on the perianal region five hours before operation.

GENTIAN VIOLET

Viola Crystallina (B.P.). It is hexamethylpararosaniline hydrochloride.

CHARACTERS. Bronze-green crystals. *Solubility.* 1 in 20 of water and 90 per cent. alcohol ; 1 in 16 of glycerin.

Dose (unofficial), 0·003—0·007 G. per kilo body weight.

Action

Medicinal gentian violet, or crystal violet, is an **antiseptic** which has a special action on Gram-positive organisms. In this respect it is highly selective, being powerfully bacteriostatic against staphylococci, diphtheroids, corynebacteria, aerobic spore-bearing bacilli and moulds, whilst seven times the concentration is needed to inhibit the growth of streptococci.

Therapeutics

Its antiseptic action (2 per cent.) is used in the treatment of **impetigo contagiosa** with excellent results. It should be reserved for the dry, scaly stage.

Gentian violet is now replacing tannic acid in the treatment of **burns.** Its coagulum is more flexible. A 2 per cent. solution should be sprayed on at two-hour intervals until a good coagulum has been formed. Gentian violet jelly (2 per cent. often combined with the antiseptic sodium ethyl mercuri-thiosalicylate, 0·02 per cent.) is excellent for prompt treatment of burns, especially for those on the face, hands and feet. Contractures follow less readily than after tannic acid. **Triple Dye** is now the most used solution for spraying on burns. It is gentian violet 2 per cent., brilliant green 1 per cent., neutral acriflavine 1 per cent. in water.

Gentian violet is very effective in the treatment of **thread-worm.** The adult dose is ½ gr. (30 mg.) thrice daily before meals for ten days. For infants it is

$\frac{1}{6}$ gr. (10 mg.) daily for each year of age up to six years. It should be given in capsules for one week.

FORMALDEHYDE

Liquor Formaldehydi (B.P.). *Synonym.* Formalin. An aqueous solution containing in 100 millilitres not less than 37 and not more than 41 grammes of formaldehyde, CH_2O.

CHARACTERS. A colourless liquid with a characteristic, pungent odour. Miscible with water and alcohol in all proportions. Caustic when applied to the skin.

Action

Formaldehyde vapour when inhaled is very irritating to the air-passages, and causes violent sneezing. Its antiseptic action is equal to that of mercury perchloride, yet it is not highly toxic to man. The germicidal effect is due to combination with the amino groups of the microbial proteins.

Therapeutics

It is not much used in surgery as it retards healing, but it is a most powerful antiseptic disinfectant and does not destroy coloured fabrics. A 2 per cent. solution may be used. Formalin 1, water 500, is an admirable wash for a foul mouth.

The vapour of formaldehyde is recommended as a disinfectant for sick rooms after illness; books and pictures are not damaged. It is best generated by volatilizing Paraform (a polymer of formaldehyde) tablets over a suitable lamp or a night light.

RESORCIN

Resorcinol (B.P.). $C_6H_4(OH)_2$.

SOURCE. Obtained by the interaction of fused sodium hydroxide and sodium metabenzene-disulphonate.

CHARACTERS. Colourless crystals. Taste sweet followed by bitterness. *Solubility.* 1 in 1 of water or alcohol. Freely in olive oil, ether, or glycerin.

Action and Therapeutics

Resorcin is as powerfully antiseptic as phenol. A solution in glycerin, 1 in 4, is excellent for removing epidermic scales in chronic skin diseases, and also for eliminating scurf of the scalp.

Acidum Sulphurosum (B.P.C.). Sulphurous Acid.

Source. An aqueous solution containing 6·4 per cent. of hydrogen sulphite H_2SO_3 corresponding to 5 per cent. by weight of sulphur dioxide, SO_2. The sulphur dioxide may be obtained by heating sulphuric acid with charcoal or sulphur.

Characters. A colourless liquid with a sulphurous odour. Sp. gr. 1·025.

Action

External. Sulphurous acid is strongly deoxidizing, and as it takes up oxygen so easily from organic bodies, it readily decomposes them, becoming itself converted into sulphuric acid, and hence is irritant, but not violently so, for the amount of sulphuric acid in proportion to the water is slight. It is a **disinfectant and deodorant,** for, in virtue of its property of absorbing oxygen, it destroys micro-organisms and arrests fermentation. When applied to the skin it is a **parasiticide.**

Internal. Highly irritating to mucous membranes.

Therapeutics

External. Sulphurous acid is chiefly used as an antiseptic, disinfectant, and deodorant. Sulphurous anhydride is employed as a disinfectant for a sick room after a patient with an infectious disease has been in it. The chimneys and windows should be stopped up. Flowers of sulphur are placed in an earthenware vessel and lighted. The door is shut, and the cracks around it pasted over. The room should be left untouched for six hours. Three pounds of sulphur should be allowed for every 1000 cubic feet. Sulphurous acid (2 fl. dr. to 1 fl. oz., 8 to 30 mils, of water) is locally applied to cure ringworm. Foul sores may be washed with it.

CHLORINE

This gas is not official under its own name, but it is officially obtained from chlorinated lime and chlorinated soda, and acidum nitro-hydrochloricum dilutum contains free chlorine.

1. Calx Chlorinata (B.P.). Chlorinated Lime. $CaCl_2O_2,CaCl_2$. *Synonym.* Bleaching powder.

Source. Pass chlorine gas over slaked lime.

Characters. A dull white powder, smelling of chlorine, which it evolves on addition of an acid or on exposure to air, for it absorbs carbonic acid gas. Contains 30 per cent. of available chlorine.

2. Liquor Sodæ Chlorinatæ Chirurgicalis (B.P.). Solution of Chlorinated Soda. *Synonym.* Dakin's Solution.

Source. Mix sodium carbonate with chlorinated lime, boric acid and distilled water.

3. Chloramina (B.P.). *Synonym.* Chloramine-T.

SOURCE. Action of sodium hypochlorite upon p-Toluenesulphonamide.

CHARACTERS. A white, crystalline powder; odour of chlorine. Loses chlorine on exposure and turns yellow. Soluble in 7 parts of water.

Action

External. Chlorine is one of the most powerful **antiseptics, disinfectants,** and **deodorizers.** Its antiseptic power is due to its replacing hydrogen in the microbial proteins and the formation of hydrochloric acid. In high concentration it produces irritation and vesication of the skin.

Internal. The inhalation of dilute chlorine gas causes a catching of the breath, sense of constriction of the chest, rapid, shallow respiration, retching, vomiting, headache and a paroxysmal cough which persists for long after exposure. It has been shown that the inhalation of even as little as 1 per cent. in air causes a rapid fall of blood pressure, respiration becomes difficult and soon ceases. The lungs after death are engorged and œdematous. Before death there are the usual signs of œdema with cyanosis, panting respiration, feeble rapid pulse, clammy skin and dilated chest veins. Treatment consists of raising the foot of the bed or stretcher, warmth, venesection, intravenous saline, and continuous inhalation of oxygen. Chlorine taken internally is converted into chlorides.

Therapeutics

Chlorine is largely used in the form of chlorinated lime to disinfect privies, drains, urinals, and swimming pools. It may be employed also to disinfect rooms after infectious diseases. All metals or articles, such as fabrics, likely to be bleached, should be covered up or removed; the windows and chimneys should be pasted up. The door is then shut, and the cracks around it are pasted over with paper. Chlorine water is sometimes employed as a wash for foul ulcers. Eau de Javelle is a solution containing sodium hypochlorite;

both these, liquor calcis chlorinatæ, liquor sodæ chlorinatæ, electrolysed salt solution and electrolysed sea water, are extremely valuable antiseptics, chiefly on account of the hypochlorites they contain, which, being decomposed by the tissues, liberate nascent chlorine. Dakin's solution is used in surgery especially for the Carel-Dakin irrigation treatment of wounds.

Eusol, used in surgery, is made by adding boric acid to a solution of chlorinated lime. It contains 0·27 per cent. hypochlorous acid.

Chloramine-T (p-toluene-sodium-sulpho-chloramide) is used as a 3 to 4 per cent. solution for surgical work, and as a 0·5 to 2 per cent. solution for a mouth wash or douche. The 2 per cent. oily solution is a spray disinfectant for the nose for carriers of the meningococcus, but many prefer dichloramine-T. All the bodies above mentioned act in virtue of their chlorine.

IODINE

Iodum (B.P.).

Source. Obtained from the ashes of seaweeds and from mineral iodides and iodates.

Characters. *Solubility.* 1 in 5000 of water; freely in alcohol (90 per cent.), ether, chloroform, or a solution of potassium iodide.

Preparations (B.P.)

1. **Liquor Iodi Aquosus.** *Synonyms.* Lugol's Solution. Liquor Iodi Compositus. Iodine, 5; potassium iodide, 10; water to produce 100.

Dose, 5—15 min. 0·3—1 ml.

2. **Liquor Iodi Fortis.** Iodine, 10; potassium iodide, 6. water; alcohol (90 per cent.), to produce 100.

3. **Liquor Iodi Mitis.** Iodine, 2·5; potassium iodide, 1·5; water; alcohol (90 per cent.), to produce 100.

Dose, 5—30 min. 0·3—2 ml.

Action

External. The actions of iodine applied externally are the same as those of chlorine, that is to say, it is powerfully **disinfectant and irritant.** Iodine applied to the skin produces a yellow stain, which can be removed by an alkali or sodium hyposulphite.

Internal. In the stomach iodine is converted into iodides (*q.v.*), and absorbed as such from the small intestine. Its action in the body is, therefore, that of iodides, in which form it is excreted chiefly by the kidneys, but also by the skin and respiratory tract. The administration of iodine increases the amount stored in the thyroid gland. In large doses in concentrated form it is powerfully irritant to the alimentary tract.

Therapeutics

External. Iodine is employed for its antiseptic properties, as Liquor Iodi Mitis which is used as a paint for the skin before operations. Preparations of iodine are used as counter-irritants. Dissolved in potassium iodide and glycerin it is used as a paint for tonsillitis (Mandel's paint). A decolorized tincture of iodine is prepared, consisting of iodine dissolved in rectified spirit, and decolorized by a strong solution of ammonia, but it contains no iodine, for iodide and iodate of ammonium are formed. Any effect it may have is due to excess of ammonia.

Internal. One or two minims of the weak liquor in half an ounce of water are often given, empirically, every half-hour in cases of vomiting, and sometimes with benefit. It has a striking effect in reducing the basal metabolic rate and symptoms of **thyrotoxicosis.** The dose is 5 minims of Liquor Iodi Aquosus taken in milk, thrice daily. This amount is increased by 1 minim per dose per diem until 60 minims are being taken daily. The beneficial effect is seldom maintained, however, and thus its administration is now usually reserved for the two weeks immediately preceding the day of operation on the thyroid gland. In cases of acute thyrotoxicosis, such as may arise in the course of exophthalmic goitre, or within a day or two following operation for this condition, the use of large doses of iodine administered per rectum (♏ xl in ⊙ss. saline) may be life-saving.

IODOFORM

Iodoformum (B.P.). SOURCE. Obtained by the action to iodine on acetone alcohol in the presence of a solution of potassium carbonate.

CHARACTERS. Small, lustrous, lemon-coloured hexagonal crystals. Has an odour like seaweed. Slightly soluble in water and alcohol, freely in fixed and volatile oils, ether, and chloroform. It contains 96·7 per cent. of iodine.

Preparation (B.P.)

Suppositorium Iodoformi. Each contains 0·2 G. (about 3 gr.) of iodoform.

Action

EXTERNAL. Iodoform has no action on the skin except in the cases of idiosyncrasy, when it produces an irritating erythema. Its antiseptic action is very slight and only due to decomposition with the liberation of iodine. It acts as a protective covering to a wound, but multiplying bacteria may be found beneath it.

INTERNAL. Poisoning may arise from the free use of iodoform on raw surfaces, and is characterized by sleeplessness, headache and anxiety. Tachycardia, hallucinations and delirium, followed by coma and death, have been described. The taste and odour of the drug are very noticeable by the sufferer.

Iodoform circulates partly unchanged but chiefly as iodides, in which form it is excreted in the urine. In the saliva, sweat and bronchial mucus, iodine can be demonstrated.

Therapeutics

Iodoform was used as a local disinfectant.

Its anæsthetic influence diminishes the pain of the sores to which it is applied.

POTASSIUM CHLORATE

Potassii Chloras (B.P.). SOURCE. Electrolysis of a solution of potassium chloride.

CHARACTERS. Colourless crystals. Taste, cool and saline. ***Solubility.*** **1 in 16 of cold water.**

INCOMPATIBLES. Easily explodes on trituration with many substances, especially sugar, sulphur, tannin, charcoal, and glycerin.

Dose, 5—10 gr. 0·3—0·6 G.

Preparation (B.P.)

Tabellæ Potassii Chloratis. Contain 5 grs.—0·3 grm. in each.

Action

Chlorate added to blood slowly changes hæmoglobin to methæmoglobin and hæmatin. Hæmolysis occurs subsequently. Large doses may produce the same effect after absorption. The accompanying symptoms are dyspnœa, cyanosis, vomiting, diarrhœa, rapid and feeble pulse, headache, coma and death. There is usually epigastric pain and partial suppression of urine which is dark reddish-brown. The loss of oxygen-carrying power of the blood is the chief factor here.

In less severe poisoning, anuria followed by methæmoglobinuria and the passage of casts of fragmented red cells, jaundice, abdominal pain, hæmatemesis and finally uræmia are observed. Death occurs in these subacute cases in three days to a week, and is referable to the blocking of the kidney tubules with the detritus of erythrocytes, and to a less extent to the methæmoglobinæmia.

The action was originally ascribed to oxidation, but it is difficult to accept this view because chlorates are very stable at body temperature. Furthermore, over 95 per cent. is excreted unchanged in the urine.

It should be noted that symptoms of poisoning seldom arise except in susceptible individuals.

Chlorates have no antiseptic effect on bacterial cultures. Their value in sore throat is possibly due to their giving up oxygen in the presence of septic material.

Therapeutics

It is used for **stomatitis, tonsillitis,** and **pharyngitis** of all varieties, either as lozenges, gargle (10 gr. (6 decigrms.) to 1 fl. oz. (30 mils) of water or decoction of cinchona), or given to be swallowed in solution, for it is then excreted by the saliva.

HYDROGEN PEROXIDE

Liquor Hydrogenii Peroxidi (B.P.). Contains 5—7 per cent. w/v of H_2O_2.

Action

Hydrogen peroxide is decomposed into water and oxygen when brought in contact with living tissues and the products of inflammation. The liberation of nascent oxygen accounts for its antiseptic action. The rapid evolution of gas may irritate the stomach if the substance is used in concentration. When injected subcutaneously, or if used to wash out serous cavities, it is quickly decomposed and gas embolism may result. This effect results in part from its absorption, unchanged, into the blood stream where it is broken down with great rapidity. The slower the decomposition, the more effective is the oxidation and disinfection. Rapid evolution of oxygen has a valuable cleansing effect.

Therapeutics

Hydrogen peroxide is used to disinfect drinking water (1 oz. to 1 pint). It is of great value in aiding the removal of dressings which have become adherent to a wound. It is also employed locally to arrest bleeding in the nature of capillary oozing. Owing to its bleaching powers it is a common ingredient of hair-washes.

Its main use lies in its application to suppurating wounds, the beneficial effect being due to the removal of pus by the gas bubbles and to antiseptic action exerted by oxygen on anaerobes.

Internally it is employed (½ oz. to the pint) to wash out the stomach in cases of chronic gastritis.

POTASSIUM PERMANGANATE

Potassii Permanganas (B.P.). $KMnO_4$.

Source. It may be obtained by the interaction of potassium chlorate, potassium hydroxide, and manganese dioxide.

Characters. Dark purple, delicate, slender prisms. *Solubility.* 1 in 20 of water; a grain gives a purple colour to a gallon of water.

Incompatibles. It is very readily deoxidized in the presence of organic matter. It is usually given as a pill or a tabella, and should be made up with kaolin or paraffin, or an explosion will very likely take place.

Dose, 1—3 gr. 60—200 mg.

Action

External. In the solid form potassium permanganate is a mild caustic and is, when kept dry, a permanent salt. Its most important action is that when moist it readily gives up its oxygen to oxidize proteins, thus combining with the proteins of micro-organisms. Its solutions, therefore, quickly turn dark brown, manganese dioxide being formed. It is consequently a **disinfectant, deodorant,** and **antiseptic.** But its action as a germicide is very limited, for it so readily gives up its oxygen to the organic substances in which the micro-organisms flourish that it very soon becomes inert.

Internal. Potassium permanganate when taken internally must be quickly decomposed, much of it being reduced before it reaches the stomach. Its oxidizing action on the gastric mucosa is liable to produce vomiting. Manganese salts are only absorbed from the intestine in extremely minute quantities.

Therapeutics

External. Although potassium permanganate is not of much practical use as a germicide, it is commonly employed as a deodorant for drains, bed-pans, to wash utensils, and to wash the hands ; for the last purpose it is suitable as being non-irritant. Condy's red fluid contains sodium permanganate. Snake and scorpion bites are treated by a ligature to prevent diffusion of the poison and making deep incisions near and rubbing in solid permanganate.

A 1 per cent. solution is applied locally for the dermatitis of poison ivy. The irritant principle is oxidized.

Internal. A 1 in 500 solution can be used as a mouth wash or gargle in foul conditions of the mouth, or as an injection in cases of foul discharges, such as may occur with vaginitis, uterine disease, or ozæna. A urethral douche of a solution of 1 in 1,000 may be used as a prophylactic for gonorrhœa as soon after exposure to infection as possible.

It oxidizes phosphorus, morphine and other alkaloids, and may therefore be used in the solution employed for gastric lavage.

BORIC ACID AND BORAX

Acidum Boricum (B.P.). *Synonym.* Boracic acid.

Source. Obtained by the action of sulphuric acid on borates. Contains not less than 99·5 per cent. of H_3BO_3.

Characters. Colourless crystals, feebly acid. *Solubility.* 1 in 25 of cold water; 1 in 3 of boiling water; 1 in 4 of glycerin; 1 in 30 of alcohol (90 per cent.). The solubility of boric acid is greatly increased by the addition of borax.

Dose, 5—15 gr. 0·3—1 G.

Preparations **(B.P.)**

1. **Glycerinum Acidi Borici.** Boric acid, 3; glycerin, 10.
Dose, 10—30 min. 0·6—2 ml.

2. **Unguentum Acidi Borici.** Boric acid, 10 per cent. in white paraffin ointment.

Borax (B.P.). $Na_2B_4O_7, 10H_2O$. *Synonym.* Sodium borate.

Source. Neutralize boric acid with sodium carbonate.

Characters. Transparent colourless crystals, alkaline, with a sweetish taste. *Solubility.* 1 in 25 of cold water; 1 in 1 of glycerin; not in alcohol.

Dose, 5—15 gr. 0·3—1 G.

Preparation **(B.P.)**

Glycerinum Boracis. Borax; glycerin. Sodium metaborate, glyceryl borate, and boric acid are formed.
Dose, 30—60 min. 2—4 ml.

Action

External. Both boric acid and borax are excellent antiseptics but feeble disinfectants. They appear in the urine within a few minutes of ingestion, but excretion is not complete for several days. Repeated small doses may therefore produce a cumulative effect. Albuminuria and malnutrition may appear after the prolonged administration of minute quantities. Boric acid has been used to preserve milk, butter, and animal food.

Internal. Borax and boric acid in large amounts are gastro-intestinal irritants. In exceptional instances, when large quantities have been applied to raw surfaces or mucous membranes, insomnia, headache, dimness of vision, depression, feeble pulse, ecchymoses, lumbar pain, albuminuria, and nausea, vomiting, diarrhœa, collapse and death have supervened. Its prolonged use internally or externally may cause alopecia, eczema and local œdema. Most of the boric acid is stored in the brain; next to this, in the liver. Harmful symptoms do not, as a rule, follow from taking food preserved with boric acid if the amount of it is under 0·1 per cent. in milk, or 8 grains to the pint.

Therapeutics of Boric Acid and Borax

Boracic lint is employed to dress wounds. A saturated solution of boric acid (4 per cent.) may be employed as an antiseptic wash. Such solutions are used for fetid perspiration of the feet, and as eye-washes. Glycerinum boracis is used for cleansing the mouth when affected by thrush.

Boric acid given internally is a urinary antiseptic, especially if the urine is alkaline. Frequently it is employed in solution for washing out the bladder.

HEXAMINE

Hexamina (B.P.C.). *Synonym.* Methenamina. *Unoff. Syn.* Urotropine. Contains not less than 99 per cent. of pure hexamethylene tetramine, $C_6H_{12}N_4$.

Dose, 10—30 gr. 0·6—2 G.

Action

Hexamine is decomposed by acids, and liberates formaldehyde on which its action depends. For the same reason it is very liable to set up strangury and cystitis. It diffuses very readily and appears in most organs and secretions, including cerebrospinal fluid and bile. Theoretically it can have no action in these alkaline fluids, but experimental evidence points to the liberation of formaldehyde in the bile, if infected.

Therapeutics

Hexamine was used as a urinary antiseptic in **pyelitis** and **cystitis.** It acts if the urine is acid, therefore acid phosphate of sodium should also be given, but not in the same mixture with urotropine, as chemical reaction occurs. Although the stomach contents are acid, sufficient escapes decomposition and is absorbed. It has been given in doses up to 100 gr. daily for **cholecystitis,** but the urine must be kept alkaline during this treatment.

CHRYSAROBIN

Chrysarobinum (B.P.C.).

Source. Goa powder, found in cavities of the tree *Andira araroba* of India and Brazil.

Characters. A light brownish-yellow crystalline powder, tasteless and inodorous. *Solubility :* Very sparingly in water, and sparingly in alcohol (90 per cent.).

Composition. A mixture of neutral bodies related to the principles of the anthracene purgatives.

Preparation

Unguentum Chrysarobini. Chrysarobin, 4 ; simple ointment, 96.

Action

External. It is a powerful **irritant** to the skin, which it stains yellowish brown. Linen is stained the same colour. (The stain may be removed by a weak solution of caustic soda or chlorinated lime.) It is antiparasitic.

Internal. It is very irritating to the stomach and bowels, causing vomiting and purging. It is excreted by the kidneys, and stains the urine yellow. It is liable to give rise to nephritis.

Therapeutics

It is used as an antiparasitic in ringworm, and in the treatment of **psoriasis.** The effect is due to its reducing action.

DITHRANOL (B.P.)

Synonym. Dioxyanthranol. $C_{14}H_{10}O_3$.

Source. Reduction of dihydroxyanthraquinone.

Characters. Yellow, tasteless powder. *Solubility.* Chloroform, acetone and fixed oils.

Preparation (B.P.)

Unguentum Dithranolis. Dithranol, 1 ; yellow soft paraffin, 999.

Action

Similar to that of chrysarobin but less toxic and therapeutically more active. Stains on clothes may be removed with organic solvents, *e.g.* petrol : on skin olive oil may be used.

Therapeutics

The ointment is used in the treatment of **psoriasis,** dermatophytosis, and alopecia areata. Skin sensitivity should be tested with a small quantity in the first place.

ICHTHAMMOL (B.P.)

Synonym. Ammonium Ichthosulphonate. *Unoff. Synonym.* Ichthyol.

Source. Destructive distillation of fossil fish deposits and treatment with ammonium sulphate and water.

Characters. Dark brown, viscous fluid of fishy odour.

Action and Therapeutics

Ichthyol has some antiseptic action and is mildly irritant to the skin. Taken internally in large quantities its irritant action produces diarrhœa.

It is used chiefly as an application to certain chronic skin diseases, such as **eczema** and acne; also for erysipelas in conjunction with glycerin; also as a vaginal tampon with glycerin in the treatment of **cervicitis.** It has been given by mouth for various diseases, but there is no reason to believe that it is effective.

CHAULMOOGRA OIL

Oleum Chaulmoogræ (**B.P.C.**). *Synonym.* Gynocardia oil. The fatty oil expressed from the seeds of *Taraktogenos Kurzii* (Burma).

Characters. A brownish-yellow oil or soft fat, with somewhat acrid taste. Soluble in ether, chloroform, or alcohol.

Composition. Its chief constituents are hydnocarpic and chaulmoogric acids, both unsaturated fatty acids, which are unique in possessing a closed five-chain carbon ring.

Oleum Chaulmoogræ (**B.P.** 1914) was called Oleum Gynocardiæ in **B.P.** 1898.

Dose, 5—15 min. 0·3—1 ml.—increased to 1 fl. dr. 4 ml. It is best given in capsules.

Ethyl Chaulmoograte, the ethyl esters of the purified acids. Pale yellow liquid.

Dose, 15 min. 1 ml.—by mouth or intramuscular injection.

Action and Therapeutics

Externally the oil is a powerful rubefacient, and may cause great pain when applied to raw places, but an ointment (3 fl. dr. to 1 fl. oz. of lanolin) has been used for very chronic psoriasis. Internally it is a gastro-intestinal irritant. It is used in the treatment of **leprosy,** but it must be continued for years and does not always cure. If given by mouth the drug should be in capsules.

Its value has been greatly enhanced by the isolation of hydnocarpic and chaulmoogric acids, because their sodium salts and esters are far less irritating than the crude oil. They can therefore be injected intramuscularly or intravenously.

The intravenous injection of a 3 per cent. solution of sodium chaulmoograte twice weekly has given excellent results in leprosy. The initial dose is 0·2 c.c., and this quantity is gradually raised to 5 c.c.

This salt is 100 times more bactericidal than phenol in relation to acid-fast bacilli, owing to its dissolving the fatty envelope in which they are enclosed.

HYDNOCARPUS OIL

Oleum Hydnocarpi (B.P.).

SOURCE. A fatty oil obtained by expression from the fresh, ripe seeds of *Hydnocarpus Wightiana.*

CHARACTERS. Yellowish oil of acrid taste. Soluble in hot (90 per cent.) alcohol; miscible with ether, chloroform and carbon disulphide.

Dose, 5—15 min., increasing gradually to 60 min. 0·3—1 ml., increasing gradually to 4 ml.

Oleum Hydnocarpi Æthylicum. The ethyl esters of hydnocarpus oil.

Dose, as for hydnocarpus oil.

Preparations (B.P.)

Injectio Olei Hydnocarpi.

Injectio Olei Hydnocarpi Æthylici.

Dose, 30 min., increasing gradually to 75 min.
2 ml., increasing gradually to 5 ml.—by subcutaneous or intramuscular injection.

Action and Therapeutics

Similar to that of chaulmoogra, which the hydnocarpus preparations are superseding in the treatment of leprosy.

Sodium Metabisulphite

Sodii Metabisulphis (B.P.). $Na_2S_2O_5$.

CHARACTERS. Colourless crystals soluble in water.

Therapeutics

A mild antiseptic used as a mouth-wash, 5 per cent., in thrush. It is used chiefly as a food preservative.

GROUP XI

Colouring Agents

COCHINEAL

Coccus (B.P.). Cochineal. The dried insect *Dactylopius coccus* containing eggs and larvæ.

COMPOSITION. The chief constituent is the glucoside *carminic acid*, $C_{17}H_{18}O_{10}$.

Preparation (**B.P.**)

Tinctura Cocci. Cochineal, 1; alcohol (45 per cent.), 10. Macerate.

Dose, 5—15 min. 0·3—1 ml.

RED POPPY PETALS

Rhœados Petalum (**B.P.C.**). Red Poppy Petals. The fresh petals of *Papaver rhœas.*

COMPOSITION. Red colouring matter, 40 per cent. This consists of papaveric and rhœadic acids. It is soluble in water. The petals contain no morphine, neither have they any narcotic properties.

Preparation

Syrupus Rhœados. Petals, 26; sugar, 72; alcohol (90 per cent.), 5; water to make 100. In hot countries the proportion of alcohol may be a little increased to prevent fermentation.

Dose, 30—60 min. 2—4 ml.

Crocus (**B.P.C.**). Saffron. The stigmas of *Crocus sativus:* aromatic odour; taste bitter; colour yellow.

Preparation

Glycerinum Croci. Powdered saffron, 1; glycerin, 40.

Uses

The above substances are employed in pharmacy to colour medicinal preparations.

GROUP XII

Substances whose Action is Physical

Cotton, Collodion, Oil of Theobroma, Soaps, and Acetone
(see also **Demulcents and Emollients**)

COTTON

Gossypium Absorbens (**B.P.C.**). *Synonym.* Cotton Wool. The hairs of the seeds of *Gossypium herbaceum* from which the fatty matter has been removed. This is commonly called "Absorbent Cotton Wool." Ordinary cotton wool is called "Non-Absorbent." It contains 10 per cent. of fixed oil.

From gossypium is made—

Pyroxylinum (**B.P.**). Pyroxylin or Dinitrocellulose, $C_6H_8(NO_3)_2O_5$. Gossypium is immersed in a mixture of sulphuric and nitric acids, and then drained and dried. Soluble in a mixture of ether and alcohol (90 per cent.). Resembles cotton wool but is harsher to touch. Highly inflammable.

Preparation (B.P.)

Collodium Flexile. *Synonym.* Collodion. Pyroxylin, 2; colophony, 3; castor oil, 2; alcohol (90 per cent.), 24; ether to 100.

Action and Therapeutics

Pyroxylin is only used to make collodion.

Collodion, when painted on the skin, rapidly dries from evaporation of the ether, and covers the skin with a thin protective film. This preparation is protective to small wounds and is used after slight operations.

OIL OF THEOBROMA

Oleum Theobromatis (B.P.). *Synonym.* Cacao butter. A solid fat obtained by expression from the seeds of *Theobroma cacao.* Chocolate is prepared from the roasted kernels of these seeds by the addition of sugar and vanilla. Cocoa is prepared from them by partly removing the oil of theobroma by pressure and then roasting and grinding the kernels.

CHARACTERS. Is of the consistency of tallow; yellowish, with chocolate-like odour. Does not become rancid on exposure to air. Melts at 30° to 33° C.

COMPOSITION. The chief constituents are—(1) *Stearin.* (2) A little olein. (3) An alkaloid, theobromine, $C_7H_8N_4O_2$.

Uses

It is used to make suppositories.

SOAP

Sapo Durus (B.P.). Hard soap. It is sodium oleate, $NaC_{18}H_{33}O_2$, containing 30 per cent. of water.

SOURCE. Action on olive oil with caustic soda.

Hard soap is used to make many pills.

Sapo Mollis (B.P.). Soft Soap. It is potassium oleate, $KC_{18}H_{33}O_2$.

SOURCE. Action on olive oil with caustic potash.

Preparation (B.P.)

Linimentum Saponis. Soft soap, 80; camphor, 40; oil of rosemary, 15; water, 170; alcohol (90 per cent.), to 1000.

Therapeutics

Hard soap has a laxative action and is often incorporated in pills containing other purgative principles. It is a useful excipient for resins and volatile oils. It is also used in the preparation of certain plasters and medicated soaps.

Soft soap is a basis for the mildly rubefacient liniment. Either soap is frequently made into a lather with about a pint of water at 38° C. and used as an enema. Soft soap is much to be preferred; about 1 fl. oz. (30 mils) is commonly used. All enemata but perhaps especially those made with hard soap, may produce an erythematous rash, probably due to the solution and consequent absorption of some fæcal toxin.

CURD SOAP

Sapo Animalis (B.P.). Curd Soap. Soap made with sodium hydroxide and a purified animal fat. It is chiefly sodium stearate.

Curd soap is contained in Extractum Colocynthidis Compositum and Linimentum Potassii Iodidi cum Sapone.

Action and Therapeutics

Curd soap is an excipient for volatile oils in the making of pills. A solution of 4 oz. curd soap, 6 oz. glycerin, water to 30 oz. is smeared over electrodes to ensure good contact. This is known as **Contact Soap.**

SODIUM LAURYL SULPHATE

Sodii et Laurylis Sulphas (B.P.). A mixture of sodium normal primary alkyl sulphates. Contained 58 per cent. of total alcohols.

Use

It is an ingredient of Cera Emulsificans.

GROUP XIII

Dyes

Methylene Blue, Indigocarmine, Fluorescein, Phenolsulphonphthalein, Dichlorophenol-indophenol

METHYLENE BLUE

Methylthioninæ Chloridum (B.P.). $C_{16}H_{18}N_3ClS$.

SOURCE. Interaction of dimethyl-phenylenediamine with thiosulphuric acid, and oxidation of the product. Contains not less than 80 per cent. of methylthionine chloride.

CHARACTERS. Dark green crystalline powder. Freely soluble in water and alcohol.

Dose, 1—5 gr. 60—300 mg.

Action and Therapeutics

Mildly antiseptic, and for this purpose has been used in cystitis in 2 per cent. solution for bladder lavage. It may also be given by mouth in capsules, for it is excreted in the urine which is coloured greenish-blue. Some is passed in the fæces which turn blue on exposure to air. It appears to reinforce the action of the cinchona alkaloids in the treatment of **malaria.** The dose suggested is 0·01 grm. for every year of age to a maximum of 0·3 grm. thrice daily for a week.

It is also claimed that this dye will eliminate **threadworm** infestation if given in doses of 3 grs. thrice daily for a week.

The drug will prevent the development of **methæmoglobinæmia** and thus the cyanosis resulting from sulphonamide therapy. If already present it can be abolished by administration of methylene blue.

Methylene blue is used principally as a test for **renal function** ; 1 mil of a 5 per cent. solution is injected intramuscularly. The urine should be a pale green within thirty minutes, and the colour deepens and becomes more blue up to four hours. After intravenous injection, coloured urine should be seen through a cystoscope to be ejected from both ureters within five minutes.

INDIGO CARMINE

Indicarminum (B.P.C.). $C_{16}H_8O_8N_2S_2Na_2$. *Synonym.* Sodium Indigotindisulphonate.

Source. Action of sulphuric acid on indigotin, neutralization with sodium carbonate and precipitation with sodium chloride.

Characters. Blue powder with coppery lustre. *Solubility.* 1 in 100 of water.

Dose, $\frac{3}{4}$**—**$1\frac{1}{2}$ **gr.** **0·05—0·1 G.**—by subcutaneous or intramuscular injection.

$\frac{1}{8}$**—**$\frac{1}{4}$ **gr.** **0·008—0·016 G.** by intravenous injection.

Therapeutics

This drug is employed to test **renal efficiency.** Ten mils of a 1 per cent. solution are injected intravenously, or 10 mils of a 0·4 per cent. solution intramuscularly. In the former case the dye should be seen through the cystoscope in three to five minutes ; in the latter, ten minutes.

SOLUBLE FLUORESCEIN

Fluoresceinum Sodium (B.P.). $C_{20}H_{10}O_5Na_2$.

Source. The di-sodium salt of fluorescein which is prepared by the condensation of resorcinol and phthalic anhydride.

Characters. An orange-red powder, odourless and tasteless. *Solubility.* 1 in 1 of water; 1 in 5 of alcohol. The solution is red with intense greenish-yellow fluorescence which is abolished by acidifying.

Therapeutics

Apart from its use as an indicator, soluble fluorescein is employed to demonstrate corneal ulcers because they take up the green colour which is evident in the solution. Intravenous injection, 20 mils of 5 to 10 per cent. solution, may be used to demonstrate cessation of life; if the circulation has not failed, the skin and eyes turn yellowish-green in a few minutes. It is alleged to increase the efficacy of X-rays if sprayed (5 per cent.) over a malignant growth before irradiation.

PHENOLSULPHONPHTHALEIN

Phenol-rubrum (B.P.C.). $C_{19}H_{14}O_5S$.
Characters. Red crystalline powder.
Solubility. 1 in 1300 of water; 1 in 350 of alcohol.

Therapeutics

Used as an indicator to determine the *p*H of fluids. Injected intravenously, 0·006 grm. in 1 mil as a test of renal function. At least 50 per cent. should be excreted in the first hour. Colorimetric estimation against a standard is made.

VITAMIN-C INDICATOR

Dichlorophenol-indophenol.
Characters. Purplish-blue powder soluble in water.

Therapeutics

Used in urinary titration to determine the amount of vitamin C excretion. A reasonably accurate estimation can be made by giving 0·3 G. ascorbic acid and testing urine passed 4 hours later. 20 c.c. of urine are added to 40 c.c. of a solution of the dye equivalent to 1 mg. vitamin C. If the blue colour disappears within ½ minute, the urine contains at least 5 mg. per cent. of vitamin C and a deficiency is improbable. Had a deficiency existed more of the test dose would have been held back in the tissues.

PART II

Substances used chiefly for their general action

GROUP I

Water, Chlorides, Urea, Suramin

Aqua Destillata (**B.P.**). Distilled water, H-O.

CHARACTERS. Colourless, odourless, and tasteless. 100 ml. evaporated to dryness leave not more than 0·001 G. of solid residue. Aqua destillata is always to be used for making up prescriptions.

Aqua Pro Injectione (**B.P.**).

SOURCE. Prepared by distillation of potable water into a sterilized glass receiver ; it is transferred to a hard glass sterilized container, and sterilized in an autoclave. It must be used within one month after its preparation.

Action

External. An indifferent bath (88°–98° F. or about 32°–37° C.), or one in which the bather feels neither hot nor cold, produces no particular effect.

Cold baths increase the production of heat, and abstract heat from the body if they are prolonged ; therefore at first the bodily temperature may rise slightly, but when the loss exceeds the production it falls. The amount of carbonic acid expired is increased. The rate of the pulse and respiration at first rises, but soon falls. The skin becomes pale, and the condition of goose-skin is seen. After the bath (the duration and temperature suitable for different persons vary widely) there is a feeling of warmth and exhilaration, and the cutaneous vessels dilate.

A warm bath if sufficiently prolonged may cause a slight rise of the bodily temperature, the skin becomes red, the pulse and respirations are more frequent, the amount of urine secreted is diminished, and after the bath there is profuse perspiration.

Internal. Warm water in large quantities may give rise to nausea and vomiting. Water is very slowly absorbed from the stomach, but quickly from the bowels, and very soon afterwards the amount of urine secreted is greatly increased, and to a less degree the amount of bile, pancreatic juice, and saliva. Moderate quantities of water promote the flow of gastric juice, but large amounts should not be drunk during meal-times, as that impairs digestion. If a considerable amount of water is drunk daily the amount of urinary nitrogen is increased and the fæcal flora diminished.

The action of water will be physically modified by the substances in solution in it, for there will be no physical interchange between isotonic solutions. But water passes from a hypotonic to a hypertonic solution, *e.g.* when red blood corpuscles are placed in a salt solution of such concentration that fluids pass from the corpuscles to it they shrink; but when they are placed in a weaker solution of such strength that fluid passes from the solution to them they swell. In the first case the salt solution is called hypertonic, in the second hypotonic as regards the corpuscles.

Such action, which is purely dependent upon physical characters, is known by pharmacologists as "salt-action." It can, in fact, be produced by any substance which can circulate in sufficient concentration, *e.g.* urea, but the majority of drugs have such profound pharmacological effects in small quantities that their physical action is not observed.

Therapeutics

External. *Cold baths* have been largely used to reduce the temperature in fever, especially **typhoid fever,** but the practice is unsound save where danger from hyperpyrexia exists. The temperature of a bath for a patient with typhoid fever should be between 68° and 58° F. (20° and 14° C.); he should be lowered into it by a sheet, and remain in ten minutes, unless before that time he shows signs of collapse; he is then lifted back to bed, where a blanket is thrown loosely over him. Or he may be sponged with cold water as he lies in bed; but both sponging and a cold pack (which consists of a sheet four folds thick wrung out in cold water and wrapped round the naked body for five or ten minutes) are inferior to a bath. **Sunstroke** may be treated by the application of cold, generally by means of ice poultices applied to the head.

Hot baths, like any other application of heat, **soothe pain,** hence they are useful for rheumatoid arthritis and colic, whether renal, biliary, or intestinal. They **relieve muscular spasm,** such as we find in stricture of the urethra, colic, laryngismus stridulus, other forms of laryngeal spasm, and infantile convulsions. They are of service in weariness from muscular or cerebral activity, and are useful in many inflammatory affections, as, for example, a cold in the head. A warm bath immediately before going to bed may sometimes cure insomnia. The subsequent **increased perspiration** makes hot baths and hot packs of value in the various forms of nephritis and chronic rheumatism. Great care must be taken after a hot bath which has been given to induce sweating to see that the patient is kept warm by being wrapped quickly in a hot blanket and put into a warm bed; if not, the cutaneous vessels soon contract, and there is no diaphoresis. A local hot bath has the same effects, but to a less degree. Sponging with hot water will, by the vascular dilatation and sweating it causes, reduce the temperature slightly in fever. Hot water, locally applied, stops bleeding.

A cold bath is one the temperature of which is below 70° F. (21° C.), one between 88° and 98° F. (32° and 37° C.) is properly speaking indifferent, but it is often called a warm bath. A tepid bath is intermediate between warm and cold. Anything above 98° F. (37° C.) is a hot bath. Few people can bear a temperature much over 102° F. (39° C.).

Internal. The chief therapeutic use of water is to reduce the viscosity of secretions and to aid elimination of waste products. Copious draughts are thus advised in the treatment of fevers, urinary calculi, pyelitis and cholecystitis.

Sodii Chloridum (B.P.). Sodium Chloride. NaCl. *Synonym.* Common salt.

SOURCE. Obtained by purifying common salt.

CHARACTERS. Small, white, crystalline grains or transparent cubic crystals. *Solubility.* 1 in 3 of cold water.

Preparations (B.P.)

1. **Injectio Sodii Chloridi.** *Synonyms.* Physiological saline solution: Normal saline solution. Sodium chloride, 9; distilled water, to 1000. The solution must be sterile. When used for intravenous injection it must be prepared with Sterilized Water for Intravenous Injections.

2. **Injectio Sodii Chloridi Composita.** *Synonym.* Ringer's solution for injection. Contains NaCl, 8·6 G.; KCl, 0·3 G.; $CaCl_2$, 0·48 G. in 1000 ml.

Action

External. Concentrated solutions withdraw fluid from the cells with which they are in contact, and some salt penetrates them. This causes shrinkage and irritation of the tissues.

Internal. The action of the stomach is similar to that on the skin, and concentrated solutions induce vomiting. Absorption is rapid from the intestine.

The advent of hypertonic solutions into the blood causes a withdrawal of lymph into the blood vessels by osmosis which is followed by increase of capillary pressure, which in turn causes an increased flow of lymph from vessels to tissues. The relative increase of salt over colloid in the blood tends to produce an increase of the various secretions which are rendered more watery in consistency. It is for this reason that sodium chloride and other bodies exhibiting marked salt-action are used to loosen tenacious sputum in bronchitis.

The deprival of salt leads to general weakness, œdema, and anæmia, a series of symptoms often seen in France before the repeal of the salt tax.

Its loss by profuse sweating causes severe abdominal cramp which can be prevented by the administration of draughts of normal saline. Stokers are very liable to such attacks. Sweat contains only 0·35 per cent. of salt and, therefore, loss in this way would result in a rise of salt-concentration in the body. This is offset, however, by the copious drinks of water taken by the sweating labourer. This causes more sweating and further loss of chloride.

Therapeutics

It is occasionally used as an emetic. Bathing in sea water acts as a mild general stimulant, and very concentrated hot salt baths, such as those of Droitwich and Nantwich, are useful for chronic rheumatism. Normal saline solution is frequently injected in cases of collapse in which the fluid in the blood-vessels is lessened, as from hæmorrhage, vomiting, or diarrhœa, often with strikingly good results. A pint or rather more is a usual quantity to employ for an adult. It may be injected into the rectum, under the skin, or into a vein, according to the urgency. A hypertonic solution (1½-3 per cent.) should be administered intravenously in cases of cholera. Five to 10 per cent. solutions have been given in this way in order to reduce the headache due to raised intracranial pressure from cerebral tumour or other cause. For the same purpose it may be employed shortly before trephining the skull.

Ten to twenty gramme doses of salt given daily are an invaluable adjunct to the cortical treatment of **Addison's disease.** They appear also to lessen the gravity of diphtheria in which disease signs of suprarenal failure are often present.

In cases of summer diarrhœa and vomiting of infants, the repeated administration of normal saline *per os* is often life-saving.

Potassii Chloridum (B.P.). Potassium chloride. KCl.

Dose, 15—30 gr. 1—2 G.

It is contained in Injection of Sodium Chloride, and of Sodium Lactate.

UREA (B.P.)

Urea. $CO(NH_2)_2$.

CHARACTERS. Colourless, prismatic crystals of saline taste. *Solubility.* 1 in 1 of water; 1 in 5 of alcohol.

Dose, 75—225 gr. 5—15 G.

Action

Even large doses have no appreciable effect on the tissues, but in the course of excretion by the kidneys it acts as a powerful diuretic. Its action is due to its retaining water which is thus prevented from being reabsorbed by the tubules.

Therapeutics

Urea is employed as a diuretic chiefly in the type of **nephritis** which is associated with anasarca. Fifteen to thirty grams daily often produce a remarkable diuresis and improvement in health. Urea is used also as a test of renal efficiency. (For details, *see* Textbooks of Medicine.)

SURAMIN

Suraminum (B.P.). A complex urea derivative. *Tr. Names.* Bayer 205, Germanin, Antrypol.

CHARACTERS. White, odourless, alkaline powder. Freely soluble in water.

Dose, 15—30 gr. 1—2 G.—intravenously.

Preparation (B.P.)

Injectio Suramini.

Dose, 15—30 gr. 1—2 G.—by intravenous njection. Must be freshly prepared.

Action

Suramin is a trypanocide and destroys *T. gambiense* and *T. rhodesiense* when injected intravenously. It is excreted very slowly. It is more effective against the latter, whereas Tryparsamide is to be preferred for the eradication of *T. gambiense.* It has also an anti-coagulant action by raising the resistance of fibrinogen to coagulation. It may produce nephritis and dermatitis.

Therapeutics

Suramin is an effective prophylactic, a single dose of 2 grms. giving protection for 3 months. It is used in the treatment of **trypanosomiasis.** An initial dose of 0·5 grm. is given intravenously in 10 per cent. solution. Thereafter 1 grm. is given twice a week up to a total of 10 grms.

GROUP II

Hydrates, Carbonates, Acetates, and Citrates of Sodium and Potassium

POTASSIUM

Potassium. Atomic weight 39·10.

When taken by the mouth, potassium salts are excreted as quickly as they are absorbed, so no effect is produced by the potassium ion, but this is really powerfully depressant to all nerve and muscle tissue, as is shown by local application or subcutaneous injection, in which case excretion is not nearly so rapid as absorption.

1. Potassii Hydroxidum (B.P.). KOH. *Synonym.* Caustic Potash.

Characters. Hard, deliquescent, corrosive white pencils. Strongly alkaline. It contains not less than 85 per cent. of pure potassium hydroxide.

Preparation (B.P.)

Liquor Potassii Hydroxidi. Solution of Caustic Potash KHO.

Characters. A colourless alkaline fluid with a soapy feel and taste.

Strength. Five per cent., 5 grs. in 110 ♏, 5 grms. in 100 millilitres of potassium hydroxide in water.

2. Potassii Bicarbonas (B.P.). Potassium Bicarbonate. $KHCO_3$.

Characters. Non-deliquescent, colourless prisms. *Solubility.* 1 in 4 of water.

Twenty grains neutralize 14 *grains of citric acid or* 15 *grains of tartaric acid.*

Dose, 15—30 gr. 1—2 G.

3. Potassii Acetas (B.P.). Potassium Acetate. $KC_2H_3O_2$.

Characters. White, very deliquescent, masses or granular particles. *Solubility.* 2 in 1 of water.

Dose, 15—30 gr. 1—2 G.

4. Potassi Citras (B.P.). Potassium Citrate. $K_3O_6H_5O_7H_2O$.

Characters. A white, deliquescent powder. Taste saline, feebly acid. *Solubility.* 10 in 6 of water.

Dose, 15—30 gr. 1—2 G.

SODIUM

Symbol, Na. Atomic weight, 23

The metal sodium as met with in commerce. It decomposes water, and must therefore be kept under naphtha.

All sodium salts act either by salt action or by the action of the other ion.

1. Sodii Carbonas (B.P.) Sodium Carbonate. $Na_2CO_3 10H_2O$. *Synonym.* Soda or washing soda.

Characters. Large crystals, transparent when fresh, but they soon effloresce, and become white on the surface. *Solubility.* 1 in 2 of cold water.

Twenty grains neutralize 9·8 *grains of citric acid or* 10·5 *grains of tartaric acid.*

2. Sodii Carbonas Exsiccatus (B.P.). Exsiccated Sodium Carbonate. Na_2CO_3. It is nearly anhydrous.

Characters. A dry white powder.

3. Sodii Hydroxidum (B.P.). Sodium hydroxide. NaOH.

Characters. White, brittle sticks. Deliquescent and corrosive. Absorbs carbon dioxide.

4. Sodii Bicarbonas (B.P.). Sodium Bicarbonate. $NaHCO_3$.

Characters. A white powder or small crystals. Slightly alkaline; not caustic. *Solubility.* 1 in 11 of cold water.

Twenty grains neutralize 16·7 *grains of citric acid or* 17·8 *grains of tartaric acid.*

Dose, 15—60 gr. 1—4 G.

Preparations (B.P.)

> **1. Tabellæ Sodii Bicarbonatis Compositæ.** *Synonym.* Soda Mint Tablets. Contain 5 gr.—0·3 G. $NaHCO_3$ in each, and oil of peppermint.
>
> **2. Injectio Sodii Bicarbonatis.** 5 per cent. w/v.

5. Sodii Citras (B.P.). Sodium Citrate. $C_6H_5O_7Na_3, 2H_2O$.

Characters. White, granular crystals. *Solubility.* 1 in 2.

Dose, 15—60 gr. 1—4 G.

Preparation (B.P.)

> **Tabellæ Sodii Citratis.** Contain 2 gr.—0·12 G. in each.

Hydrates and Carbonates

Action

These substances when administered by mouth owe their action to the non-metallic ion — OH. In the case of the carbonate and bicarbonate, the initial dissociation is into potassium or sodium and — CO_3, but the last combines with the hydrogen of water to form HCO_3, liberating — OH. This would suggest that the effect of administration of hydrates and carbonates would be exactly the same, but the latter are less rapidly dissociated and, less — OH being formed, are thus less powerful in action. It is essentially the alkalinity of these substances, therefore, which is responsible for their pharmacological action.

External. Apart from the neutralization of acid, the important local effect of the hydrates and carbonates is due to their solvent action on proteins, and to a slight degree, to their saponifying fat. Even weak solutions of the hydrates, if left long in contact with tissues, will cause considerable destruction, and strong ones cause sloughing for some depth because of the great penetrative power.

Internal. By dissolving the superficial layers of the mucous membrane of the mouth and tongue all the normal fur disappears, and the interior of the mouth looks red and, if the solutions be strong, it becomes irritated and very painful. Depending upon the degree of concentration and total quantity, the gastric mucous membrane may be either severely and extensively damaged with perforation of the wall, or in mild cases the lower part of the œsophagus and the stomach may be so inflamed that subsequently gross distortion occurs owing to scar formation. In medicinal doses the only effect is a partial, or complete, neutralization of the acidity of the gastric juice. The mucus of the stomach is rendered less viscid, or even completely dissolved by them. Here again, the action of the carbonates and especially the bicarbonates is much milder than that of the hydrates. All alkalies tend to accelerate the emptying of the stomach and are thus liable to give rise to diarrhœa. It is unlikely that in medicinal doses they have any effect upon the intestinal digestion. The secretion of bile is unaffected by their administration, but it may be rendered less viscid by simple salt-action.

Absorption takes place rapidly from the upper alimentary tract and the alkalies are then promptly neutralized by carbonic acid and circulate as neutral bicarbonates. This increases the alkali reserve with a consequent reduction of CO_2 tension in the blood, and a rise in the alveolar air. Given repeatedly in large doses the condition of alkalosis may arise. The ammonia output in the urine is diminished, whilst the urea excretion is increased, the reason being that the ammonia which is normally needed for the neutralization of acid products is less in demand on account of the supply of fixed alkalies.

Excretion takes place rapidly through the kidneys, the urine becoming less acid, or even alkaline, and is then found to contain bicarbonate of potassium or of sodium. About 200 grains of the carbonate will usually keep the urine alkaline if it be given in divided doses over twenty-four hours. The salt-action effect produces some diuresis.

Therapeutics

External. The hydrates in the form of pencils have been used to remove warts and effect some degree of cauterization for other conditions. They have been largely superseded by diathermy and X-ray and radium applications, however. The carbonates are used in dilute form for baths, owing to their slight irritant effect on the skin and beneficial influence on the circulation.

Internal. The hydrates are seldom used internally, but the carbonates are used frequently, chiefly in order to neutralize excessive acidity in the gastric juice. They are employed for simple hyperchlorhydria, and still more for the treatment of **duodenal ulcer.** Whereas prompt relief is given by sodium or potassium bicarbonate, the objection to their use alone is that the evolution of CO_2 causes distension and irritation of the stomach and leads to a later rise of acidity. It is usual now to combine the carbonates and bicarbonates, a powder consisting of magnesium carbonate, five parts, calcium carbonate five parts, and sodium bicarbonate one part forms the basis of many popular and efficacious remedies for these conditions. The carbonates have a more prolonged action without the unpleasant effects of the bicarbonates, and the proportion of the calcium salt is varied according to whether there is diarrhœa or not. The astringent effect of calcium is utilized for this by increasing its proportion in the mixture. A 5 per cent. solution of sodium bicarbonate may be employed to wash out the stomach, especially when it is the seat of chronic inflammation associated with excess of mucus. Similarly, for chronic **gastritis** it is common not only to practise lavage, but to administer the bicarbonate as a long drink before the first meal of the day in order to render the mucus less tenacious. The same solution may be employed in washing out the bladder for certain cases of cystitis. In acidosis, especially that associated with diabetes, the administration of bicarbonate of soda either by mouth or, failing this, intravenously in 5 per cent. solution is of value. Not more than 20 grammes should be given because excess may cause alkalosis. Alkaline drinks have for centuries been a popular remedy in various pyrexial conditions and in rheumatism, but in both states it is probable that the action is largely due to a flushing out of the tissues with fluid, and to a less extent to the alkalinity.

To render the urine alkaline, carbonates and bicarbonates are given frequently, especially if combined with potassium citrate. They are indicated for pyelitis, cystitis and the form of **nephritis** associated with œdema. Very large doses of bicarbonate are used in the last-named condition, and a careful watch has to be kept upon the plasma bicarbonate to avoid over-dosage with aggravation of the œdema.

Sodium bicarbonate is given with salicylate in **rheumatic fever,** in the proportion of 2 parts to 1. Its action is to protect the stomach from salicylate irritation and to reduce or prevent the toxic effects of acidosis due to salicylate.

The carbonates are frequently used as antidotes to poisoning with mineral acids, but magnesium oxide, though usually less readily available, is to be preferred for this purpose.

Poisoning with caustic alkalies should be treated by the administration of dilute organic acid, *e.g.* vinegar.

Citrates and Acetates

Action

External. No action except that due to their properties as salts.

Internal. The acetates and citrates are rapidly absorbed and almost completely oxidized to carbonates in the tissues. They act, therefore, like carbonates and bicarbonates in every way except before absorption, for they do not neutralize the gastric juice.

Therapeutics

Owing to salt-action they are used as mild saline expectorants, diaphoretics and diuretics. Potassium citrate is a more powerful **diuretic** than sodium citrate. Their chief value is to render the urine alkaline. Sodium citrate, owing to its power of combining with calcium, is employed to prevent the curdling of milk into dense masses, and the coagulation of blood taken for transfusion.

GROUP III

AMMONIUM

Symbol, NH_4

1. **Liquor Ammoniæ Fortis (B.P.).** Strong Solution of Ammonia. NH_3 (32·5 per cent. dissolved in water).

CHARACTERS. A colourless liquid, of a very pungent odour, and very alkaline.

Preparations (**B.P.**)

1. **Linimentum Camphoræ Ammoniatum,** *see* Camphor.

2. **Liquor Ammoniæ Dilutus (B.P.).** Solution of Ammonia. NH_3 (10 per cent. dissolved in water).

SOURCE. Mix strong solution of ammonia, 1 part, and distilled water, 2 parts.

3. **Spiritus Ammoniæ Aromaticus.**

Dose, 50—60 min. 1—4 ml.

2. **Ammonii Bicarbonas (B.P.).** Ammonium bicarbonate. NH_4HCO_3.

CHARACTERS. White, crystalline, hygroscopic powder. Slightly ammoniacal odour. *Solubility*: 1 in 5½.

Dose, 5—10 gr. 0·3—0·6 G.

Preparation (B.P.)

Spiritus Ammoniæ Aromaticus. *Synonym.* Spirit of sal volatile. Ammonium bicarbonate, 25; Liquor Ammoniæ Fortis, 60; oil of nutmeg; oil of lemon; alcohol, 750; water, 1000.

Dose, 15—60 min. 1—4 ml.

3. **Ammonii Chloridum** (**B.P.**). Ammonium Chloride. NH_4Cl. *Synonym.* Sal ammoniac.

CHARACTERS. Colourless crystals, volatile. *Solubility*: 1 in 3 of water.

Dose, 5—60 gr. 0·3—4 G.

4. **Liquor Ammonii Acetatis Fortis** (**B.P.**). Strong solution of Ammonium Acetate.

Dose, 15—60 min. 1—4 ml.

5. **Liquor Ammonii Acetatis Dilutus** (**B.P.**). Solution of Ammonium Acetate. *Synonym.* Minderer's spirit.

SOURCE. Strong solution of ammonium acetate, distilled water. Strength 1 in 8.

Dose, ½—1 fl. oz. 8—30 ml.

Action

External. A solution of ammonia produces **rubefaction,** with a sensation of heat, and, if strong, a sensation of pain and burning. If the vapour is confined it causes vesication.

Internal. When inhaled, the vapour of ammonia is irritating to the nose and air passages, causing a pungent sensation and sneezing. The eyes and nose water. Reflex stimulation of the medullary centres causes temporary arrest followed by deepening of respiration, rise of blood-pressure, and slowing of the heart. If very concentrated it produces swelling and inflammation of the nose, glottis, and respiratory tract. Spasm of the glottis may kill.

As an alkali ammonia acts like the other alkalies.

Ammonia and ammonium carbonate are converted by the liver to urea, which is excreted by the kidneys. Ammonium chloride is largely changed to urea and HCl is liberated. This **reduces the alkali reserve** of the blood and produces diuresis. Organic salts such as the citrate and acetate are partly converted to urea, the acid radicle being oxidized to carbonic acid partly excreted unchanged.

Therapeutics

External. The liniment is used as a counter-irritant in conditions such as chronic rheumatism. Ammonia is a very uncertain vesicant. Weak solutions are applied to the bites produced by insects to relieve itching. Liquor ammoniæ dilutus is a valuable restorative in fainting if the vapour be inhaled.

Internal. The carbonates are used chiefly as reflex **expectorants** in bronchitis but are probably useless. They also act as **diuretics** owing to their conversion to urea. The acetate is employed as a **diuretic,** for it has no appreciable irritative action on the stomach and is, therefore, useless as an expectorant. The carbonate, if sufficiently concentrated, is an **emetic.** Spiritus Ammoniæ Aromaticus is inhaled for its reflex effects, and is taken as a carminative in dyspepsia.

Ammonium chloride is given by the mouth as an **expectorant.** Clinical investigation suggests that for this purpose therapeutic doses are useless.

To **enhance the effect of mercurial diuretics** ammonium chloride is given at four and two hours preceding each injection, in doses of 1 grm. in cachet.

The drug is also given for **chronic lead poisoning** for the acidosis it produces hastens the withdrawal of the metal together with calcium from the bones.

GROUP IV

Saline Diuretics

Nitrates (*see also* Sodium Sulphate)

Potassii Nitras (B.P.). KNO_3 *Synonyms.* Nitre; Saltpetre. CHARACTERS. White six-sided prisms. Taste, cool, saline. *Solubility*: 1 in 4 of water.

Dose, 5—15 gr. 0·3—1 G.

Action

Internal. Nitrates in concentrated solution are irritants, and therefore potassium nitrate is liable to cause nausea, vomiting, diarrhœa, symptomatic of the **gastritis** and **enteritis** produced by it. The nitrates of the alkalies have a saline taste. Potassium nitrate is the salt usually employed and in ordinary doses acts as a **diuretic** only. This is due to salt-action exciting exchange of fluid between blood and lymph and therefore promoting filtration in the kidney. The nitrate and potassium ions in the filtrate retard reabsorption of water in the tubules. Nitrates are more powerfully diuretic than chlorides, and potassium more than sodium.

Nitrates are excreted in the urine unchanged and to a less extent in the saliva and sweat partly as nitrite. Some may be converted to nitrite in the body.

Therapeutics

Nitrates are sometimes employed as a **diuretic** and diaphoretic in febrile conditions, but the acetate and the citrate are preferable.

For the treatment of **asthma,** blotting paper is soaked in a 20 per cent. solution of nitre. When dry, it is lighted and the patient inhales the fumes. The action is due to the liberation of nitrites. This treatment often relieves, and nitre is a common ingredient of asthma powders.

GROUP V

Calcium and Barium

These drugs form only few soluble salts, and even they penetrate the tissues with difficulty. They cause precipitation of proteins if in fairly concentrated solution, and this accounts for the pain, and possibly sloughing, following their injection subcutaneously and intramuscularly.

CALCIUM

Calcium Carbonate is pharmacopœial in two forms.

1. Creta (B.P.). Prepared Chalk. $CaCO_3$.

Source. Native calcium carbonate freed from most of its impurities.

Characters. White friable pieces or a dull white powder. Insoluble in water.

Incompatibles. Acids and sulphates.

Dose, 15—60 gr. 1—4 G.

Preparations (**B.P.**)

1. Hydrargyrum cum Creta, *see* Hydrargyrum.

Dose, 1—5 gr. 60—300 mg.

2. Pulvis Cretæ Aromaticus. Prepared chalk, 25; cinnamon, 10; cloves, 4; cardamom seeds, 3; nutmeg, 8; sugar, 50.

Dose, 10—60 gr. 0·6—4 G.

3. Pulvis Cretæ Aromaticus cum Opio, *see* Opium.

Dose, 10—60 gr. 0·6—4 G.

2. Calcii Carbonas (B.P.). Precipitated Calcium Carbonate. $CaCO_3$. *Synonym.* Precipitated chalk.

Source. Boil together solutions of calcium chloride and sodium carbonate.

Characters. A white crystalline powder insoluble in water.

Dose, 15—60 gr. 1—4 G.

3. Calcii Hydroxidum (B.P.). Calcium Hydroxide. *Synonym.* Slaked Lime. $Ca(OH)_2$.

Source. Prepared by the interaction of water and calcium oxide.

Characters. A white, strongly alkaline powder. *Solubility:* 1 in 900 of cold water; if sugar be added 1 in 60.

Preparation

Liquor Calcii Hydroxidi (B.P.). *Synonyms.* Aqua calcis, Lime water. *Strength* 0·1 per cent.

Dose, 1—4 fl. oz. 30—120 ml.

4. Calcii Phosphas (B.P.). Calcium Phosphate. $Ca_3(PO_4)_2$. *Synonym.* Phosphate of lime.

Characters. A light white amorphous powder, insoluble in water.

Dose, 10—30 gr. 0·6—2 G.

5. Calcii Chloridum (B.P.). Calcium Chloride. $CaCl_2$.

Characters. White masses, having a great affinity for water, and so deliquescent that they cannot be easily weighed. Should be kept in solution. Soluble in its own weight of water.

Dose, 10—30 gr. 0·6—2 G.

6. Calcii Chloridum Hydratum (B.P.). Hydrated Calcium Chloride. $CaCl_2, 6H_2O$.

Characters. Colourless crystals: very deliquescent.

Dose, 10—30 gr. 0·6—2 G. by intravenous injection.

7. Calcii Gluconas (B.P.). Calcium Gluconate. $C_{12}H_{22}O_{14}Ca_1H_2O$.

Source. Combination of calcium and gluconic acid. Contains ·9 per cent. of Ca.

CHARACTERS. Crystalline or granular tasteless powder. *Solubility* : 1 in 30 of water.

Dose, 15—60 gr. 1—4 G.

Preparation (**B.P.**)

Injectio Calcii Gluconatis. Contains 10 grms. calcium gluconate in 95 mils of distilled water, *i.e.* a supersaturated solution.

Dose, 150—300 min. 10—20 ml.

8. **Calcii Lactas** (**B.P.**). Calcium lactate, $Ca(C_3H_3O)_2.5H_2O$. CHARACTERS. A white powder ; almost tasteless. *Solubility* : 1 in 18·5 parts of water.

Dose, 15—60 gr. 1—4 G.

Preparation (**B.P.**)

Tabellæ Calcii Lactatis. Contain 5 gr.—0·3 G. in each.

9. **Calx Sodica** (**B.P.**). Soda Lime. A mixture of sodium hydroxide with calcium hydroxide. It absorbs not less than 20 per cent. of its weight of CO_2.

Action

The body contains about 2 per cent. of calcium, over 90 per cent. of which is in the bones and teeth. The total amount of the element in the blood and tissue fluids is about 2 grms., but this small amount is essential for the maintenance of life.

Absorption. Even the soluble salts, viz., lactate and chloride, are absorbed with difficulty from the intestine where they are precipitated as the insoluble phosphate and carbonate, thus exerting an astringent action. About half the quantity taken passes out in the stools, whilst the remainder is absorbed and circulates partly as bicarbonates but chiefly in combination with protein. Only the former ionized form is physiologically active. The quantity of combined and free calcium in the blood is 10 mgm. per 100 c.c. ; 2 mgm. exist as free ions whilst 5–6 mgm. can pass a dialysing membrane, and this quantity is thus found in 100 c.c. of cerebro-spinal fluid. Where the body is deprived of vitamin D the absorption of calcium is deficient, and symptoms of rickets are liable to arise.

When administered by mouth, calcium has no obvious effect except that of producing constipation. Intravenous injection may produce muscular hypotonia by depression of the neuromuscular connections in striated muscle. The heart-beat is accelerated and strengthened by small quantities (10 c.c. of 10 per cent. solution), but arrested by larger doses, which also produce myosis by action on the iris. A sensation of burning is complained of soon after injection is started, and lasts for ten minutes.

Antagonism. The general action of calcium is antagonized by potassium. Calcium completely antagonizes the depressant action of magnesium on the central nervous system.

Excretion. Calcium is excreted through the large intestine as the phosphate and carbonate, and by the kidneys in the form of chloride. Most passes by the former route, but excess of chlorides in the body fluids increases the output of the corresponding soluble salt in the urine. The administration of magnesium hastens the excretion of calcium, and *vice versâ.*

Therapeutics

External. Prepared chalk is used as a dusting powder. Slaked lime is caustic, whilst lime water is astringent. The former has been used in the form of Vienna paste to destroy warts, whilst the latter is employed as an astringent to ulcers and burns (" Carron Oil "). Lime water is also used in the preparation of milk for infant feeding, as it reduces the size of the curds.

Internal. Calcium carbonate is extensively employed in conjunction with the corresponding magnesium compound as an antacid in the treatment of **gastric** and **duodenal ulcer.** Its astringent action counterbalances the laxative effect of magnesium carbonate, whilst the slower evolution of carbon dioxide offers an advantage over the hitherto popular sodium bicarbonate. Calcium phosphate, pure or mixed with tribasic calcium phosphate (which is unobtainable in pure form), $Ca_3(PO_4)_2$, is a valuable antacid for the treatment of peptic ulcer. It is usually combined with tribasic magnesium phosphate. These salts have the advantage over the carbonates in not producing eructation from CO_2 evolution and in not causing alkalosis (*cf.* aluminium hydroxide).

The more soluble calcium lactate is still administered in conditions of calcium deficiency, *e.g.* **rickets**, tetany and pregnancy. The absorption of calcium is favoured by the administration of vitamin D. Since the *rôle* played by vitamin D has been recognized in relation to rickets, the disease and the calcium deficiency have been adequately treated with this vitamin or exposure to sunlight.

The intravenous or intramuscular injection (1 grain in 100 minims of water) of calcium chloride will relieve the **tetany** of parathyroid disease, and possibly reduces the tendency to bleeding in **jaundice** (*see* vitamin K). For the latter purpose 10 c.c. of a 10 per cent. solution should be administered strictly intravenously. If a feeling of heat is then experienced all over the body, the coagulation time of the blood will be found to return to normal. It remains so for several days. The relationship of the symptom to the effect is unexplained.

The hydrated calcium chloride of the B.P. has to be dispensed in the place of calcium chloride if ordered for injection. Twice the quantity must be given.

Calcium gluconate is less irritant than the other salts and is therefore safer to administer intramuscularly (5 to 10 per cent.) than the chloride. It may be given intravenously and is probably well absorbed when taken by mouth, especially when given in conjunction with vitamin D.

Uræmia when accompanied by a lowered blood-calcium and consequent muscular twitchings may be mitigated by intravenous injections of calcium gluconate (10 mils of 10 per cent.).

In the treatment of chronic **lead poisoning** with ammonium chloride, calcium is withdrawn from the bones. At intervals the process must be reversed and calcium gluconate and vitamin D are administered in order to replace the loss of osseous calcium which necessarily accompanies withdrawal of lead deposits.

Calcium protects the liver against carbon tetrachloride (*q.v.*) and should, therefore, be given in the treatment of **hook-worm**.

There seems to be some clinical evidence of the value of calcium administration in **urticaria** and **chilblains.** It is explained as being due to the action of reducing permeability of the capillary walls.

Barium

Barii Chloridum. Barium Chloride. $BaCl_2,2H_2O$.

CHARACTERS. Colourless, translucent tables.

It is in the Appendix of the Pharmacopœia, as an aqueous solution, used for testing, but it may be given internally.

Dose, ½—2 gr. 0·03—0·12 G.

Action

Barium salts cause the cardiac contractions to become slower and more forcible, acting like digitalis. The blood vessels all over the body, including those of the lungs, are constricted by direct action on their muscle, and blood pressure rises; the bronchioles too are constricted. The plain muscular fibres of the intestine may be excited, and then peristalsis being increased diarrhœa ensues. In these respects barium resembles ergot as well as digitalis. It acts like veratrine when applied locally to voluntary muscles, prolonging the contraction. This effect is neutralized by the application of potassium salts.

Barii Sulphas (B.P.). Barium sulphate.

CHARACTERS. A heavy, white odourless powder. Insoluble in water.

Uses

It is employed to outline the alimentary tract and pathological sinuses in X-ray work. It is mixed with water to produce a consistency requisite for the particular examination.

Baryta Sulphurata (B.P.C.). Barium sulphide, from ½ to 3 parts, with wheat starch 3 parts, made into a cream with water, spread on the skin, left for five or ten minutes, and then removed with a blunt knife, forms a good **depilatory.** It acts by dissolving the hair shafts, but does not destroy the roots.

Toxicology

Several outbreaks of barium poisoning have been recorded. Soluble barium salts such as the chloride or carbonate may be mistakenly used in the place of the sulphate in X-ray work. The carbonate has been fraudulently employed as a diluent of flour. The chloride is a heavy contaminant of salt obtained from the mines of Szechuen giving rise to transient paralysis, similar to the familial periodic variety, known locally as **Pa Ping.**

Nausea, vomiting, diarrhœa, abdominal pain appear within an hour of taking the drug. In about 3 hours after some slowing of the pulse (not bradycardia) due to extrasystoles, there develops sluggish pupillary reaction, loss of convergence, varying degrees of motor paralysis and diminution of tendon reflexes—both chiefly affecting the extensors—no sensory loss, and pulse-heart ratio 40/80. Recovery usually starts in 4 hours from the onset and is complete in 36 hours. In more severe cases total paralysis of the limbs and weakness of the muscles of respiration may be seen on the second and third day. Death is rare and may be due to direct action on the heart, or to paralysis of the respiratory muscles.

Treatment. Sodium or magnesium sulphate should be given promptly in full doses to encourage precipitation of the insoluble barium sulphate.

Muscular paralysis should be treated with 5 per cent. potassium citrate, 150 mils intravenously.

GROUP VI

Acids

The substances described in this section owe their action chiefly to their acidity. Acids such as hydrocyanic, tannic, and salicylic are described under appropriate headings.

1. **Acidum Sulphuricum (B.P.C.).** Sulphuric Acid contains not less than 95 per cent. of hydrogen sulphate, H_2SO_4.

Acidum Sulphuricum Aromaticum (B.P.C.). *Synonym.* Elixir of vitriol. Sulphuric acid, 70 ; spirit of cinnamon, 15 ; tincture of ginger, 250 ; alcohol (90 per cent.), to produce 1000. Sp. gr. 0·917 to 0·923. It contains much ethyl sulphuric (sulphovinic) acid.

Dose, 5—20 min. 0·3—1·2 ml.

2. **Acidum Nitricum (B.P.).** Nitric Acid contains 70 per cent. of hydrogen nitrate, and 30 per cent. of water.

3. **Acidum Hydrochloricum (B.P.).** Hydrochloric Acid.

CHARACTERS. A colourless, very acid, fuming liquid.

Preparation (**B.P.**)

Acidum Hydrochloricum Dilutum. Hydrochloric acid distilled water. Approx. 10 per cent. of HCl.

Dose, 10—120 min. 0·6—8 ml.

4. **Acidum Phosphoricum (B.P.).** Concentrated Phosphoric Acid is a liquid containing 89 per cent. of H_3PO_4.

SOURCE. Obtained by the oxidation of phosphorus in contact with water.

CHARACTERS. A colourless syrupy liquid, of a sour taste.

Preparation **(B.P.)**

Acidum Phosphoricum Dilutum. Concentrated phosphoric acid; water. It contains 10 per cent. of hydrogen orthophosphate.

Dose, 5—60 min. 0·3—4 ml.

5. Sodii Phosphas Acidus (B.P.). *Synonym.* Sodium dihydrogen phosphate. Contains not less than 98 per cent. of $NaH_2PO_4,2H_2O$.

CHARACTERS. Rhombic, colourless, crystals. *Solubility* : **1 in 1** of water.

Dose, 30—60 gr. 2—4 G.

6. Acidum Hypophosphorosum Dilutum (B.P.). Dilute hypophosphorous acid.

Dose, 5—15 min. 0·3—1 ml.

7. Acidum Aceticum (B.P.). Acetic Acid.

SOURCE. Obtained from wood by destructive distillation and purification, or from ethylic alcohol by oxidation.

CHARACTERS. A colourless liquid. Contains 33 per cent. of hydrogen acetate.

Preparations **(B.P.)**

1. Acidum Aceticum Dilutum. Acetic Acid diluted with distilled water. Contains 6 per cent. of hydrogen acetate.

2. Oxymel. Acetic acid, 15; water; purified honey, to 100.

Dose, 30—120 min. 2—8 ml.

8. Acidum Aceticum Glaciale (B.P.). Glacial Acetic Acid.

CHARACTERS. A colourless very acid liquid. Contains not less than 99 per cent. of hydrogen acetate, $HC_2H_3O_2$.

9. Acidum Trichloraceticum (B.P.). Trichloracetic acid.

SOURCE. Action of nitric acid on chloral. Contains 98 per cent. of $C_2HO_2Cl_3$.

CHARACTERS. Colourless, deliquescent crystals of pungent odour. Freely soluble in water.

10. Acidum Citricum (B.P.). Citric Acid, Hydrogen Citrate.

SOURCE. Obtained from the juice of the fruits of various species of Citrus, and contains not less than 99·5 per cent. of hydrogen citrate, $H_3C_6H_5O_7$, H_2O.

CHARACTERS. Large colourless trimetric prisms, very soluble in water. **35 grs. to 1 fl. oz.** of water make a solution the **same average strength as lemon juice, and neutralize 50 grs. of potassium bicarbonate, 42 grs. of sodium bicarbonate, or 26 grs. of ammonium carbonate.** Citric acid, like tartaric acid, is often used to produce an effervescing mixture with one of the above carbonates, the two solutions being mixed immediately before taking. The carbonic acid gas which causes the effervescence is formed thus :—$3KHCO_3 + H_3C_6H_5O_7 = K_3C_6H_5O_7 + 3CO_2 + 3H_2O$.

Dose, 5—30 gr. 0·3—2 G.

11. Acidum Tartaricum (B.P.). Tartaric Acid. It contains not less than 99 5 per cent. of hydrogen tartrate.

SOURCE. Prepared from potassium acid tartrate.

CHARACTERS. Colourless opaque monoclinic prisms, longer than those of citric acid. Very soluble in water. **35 gr. neutralize 46 gr. of potassium bicarbonate, 38 gr. of sodium bicarbonate, or 24½ gr. of ammonium carbonate.**

Dose, 5—30 gr. 0·3—2 G.

12. Acidum Lacticum (B.P.). Lactic acid is an aqueous solution containing not less than 87·5 per cent. of hydrogen lactate, $HC_3H_5O_3$.

SOURCE. It may be made by the fermentation of lactose.

CHARACTERS. A colourless syrupy liquid. Mixes well with water, alcohol, and ether.

Preparation (B.P.)

Injectio Sodii Lactatis Composita. *Synonym.* Hartmann's Solution: Ringer-Lactate Solution. Contains lactic acid, sodium chloride and hydroxide, potassium and calcium chloride.

Action

External. All these acids are **irritants** when applied externally. The feeblest is citric. Its concentrated solution has no action on the sound skin, but is irritant to mucous membranes and abraded surfaces. Tartaric is stronger than citric acid; it will act upon the unabraded skin, and applied to a sore it produces pain, a sensation of burning, and considerable vascular dilatation. The remaining acids are powerful irritants, therefore even weak dilute solutions of them may produce considerable redness and perhaps vesication, and when the solution is strong they are very energetic **caustics**; sulphuric and phosphoric acids, having a powerful affinity for water, are especially active. Sulphuric acid produces a white eschar which turns to black; nitric stains the skin a deep yellow owing to the formation of nitro-derivatives of tyrosine; it does not redissolve the albumen it precipitates, and it is consequently limited in its area of action; nitro-hydrochloric is very powerful;

hydrochloric is the least active of the mineral acids; glacial acetic acid is useful when a limited action is required; lactic acid is caustic to mucous surfaces and of low toxicity: trichloracetic acid is a much more powerful irritant, acting rapidly as an escharotic. All the stronger acids unite with and **coagulate albumen**; hence weak solutions act as **astringents** and **hæmostatics.** Dilute solutions of acids are cooling to the flushed skin of fever, therefore they are called **refrigerants.** Acids are general protoplasmic poisons, hence they are **antiseptic.**

Internal. *Mouth.* All acids have a peculiar taste, and give rise to a feeling of roughness about the teeth. With regard to the saliva they **increase the amount secreted,** consequently by keeping the mouth moist they allay thirst.

Stomach. Acids cause coagulation of the superficial layers of proteins, and extensive destruction in concentrated form.

Pancreas. Acids experimentally placed in, or passed from the stomach into, the duodenum convert the prosecretin existing in the duodenal mucous membrane into secretin, and, this being absorbed into the blood, excites the pancreatic flow.

Intestine. Acids quickly become converted into neutral salts, and are probably mainly absorbed as such. Some, especially sulphuric (diluted), are believed to preserve in the intestine their astringent action. The presence of acids in the duodenum leads to reflex closure of the pylorus.

Remote effects. Inorganic acids **lower the alkali reserve** of the blood. They are absorbed as neutral and acid salts. The latter are at once neutralized by the $NaHCO_3$ of the plasma with loss of CO_2 by the lungs. The raised H-ion concentration is promptly corrected by the kidneys excreting acid salts, *e.g.* acid sodium phosphate. In man and the carnivora these acids are also neutralized by ammonia and thus excreted in the urine, so that the ammonia nitrogen ratio rises. Acetic, citric, lactic, and tartaric acids are mainly oxidized in the body to carbonates and **increase the alkali reserve.**

Large doses of mineral acids increase respiration and produce a comatose condition in herbivora by the production of acidosis. In carnivora this result is very difficult to obtain owing to the neutralization of the acid by ammonia.

Therapeutics

External. Nitric acid is more often used as a caustic than the others, for, owing to their great affinity for water, it is difficult to limit the action of sulphuric and phosphoric acids; and the remaining acids are not so powerful as nitric acid. It is employed to destroy warts, condylomata and cancrum oris. Glacial acetic acid is used for small warts and corns. If this causes pain it may be diluted. Dilute hypophosphorous acid acts like any other feeble acid, and is used as a preservative in Syrupus Ferri Iodidi. Any well-diluted acid, especially sulphuric, may be applied to check slight bleeding, as that of leech-bites and piles. In fever the skin is bathed with vinegar as a refrigerant.

Trichloracetic acid is used to destroy warts and has been recommended for application to rodent ulcers with which it is left in contact for three minutes. The resulting eschar peels off in three weeks and may be replaced by a sound scar. Five per cent. solutions may be used for the local treatment of infected tonsils, and are effective in Vincent's angina. A 25 per cent. solution will remove tobacco stains from the teeth. Caution must be exercised in its use.

Internal. *Mouth.* As acids damage the teeth they should be taken through a glass tube. Lemon juice or citric acid itself is often used to stimulate the secretion of saliva, and hence allay the thirst of fever patients.

Stomach and intestines. Hydrochloric acid is of value to that variety of dyspepsia in which the acidity of the gastric juice is deficient. It is of special value in correcting the **diarrhœa** which often accompanies achlorhydria. Thirty minims of the dilute acid in a wineglassful of orangeade and sipped with meals usually suffice. Dilute sulphuric acid is successful as an astringent in many cases of summer diarrhœa. It is often taken by workers in lead factories, as it forms an insoluble sulphate of lead in the intestines, and so prevents absorption of lead.

Phosphoric acid and acid sodium phosphate may be used to render the urine acid. They are thus employed in conjunction with hexamine.

Soured milk is occasionally of benefit in summer diarrhœa and colitis. It may then be drunk like ordinary milk—two or three pints a day for an adult—and the still active lactic acid bacilli in it inhibit the growth of intestinal micro-organisms and the lactic acid formed from the lactose in the milk acts as an intestinal disinfectant.

Remote effects. The remote effects of salts of citric, tartaric, and acetic acids have been described elsewhere. They are due to the increase in the alkalinity of the blood and the urine.

Toxicology of Acids

All these acids are severe gastro-intestinal irritants when given in toxic doses. Tartaric, citric, lactic and mandelic are far less irritant than the others mentioned and are not used as poisons. The symptoms produced by the whole class are severe burning pain extending from the mouth to the stomach, excoriation of the mouth with the formation of sloughs, great difficulty in swallowing, vomiting of dark brown coffee-coloured material and shreds of mucus, intense abdominal pain aggravated by the slightest movement, generally obstinate constipation, but if the bowels are open the motions are dark, from the blood contained in them. Some of the acid generally passes down to the larynx and causes swelling of that organ, and consequently dyspnœa from obstruction to respiration. The patient becomes cold, collapsed, and covered with a cold sweat ; his pulse is very feeble, and he suffers from great thirst. *Post mortem.* The mucous membrane of the mouth and gullet is softened and corroded, and whitish-grey sloughs and hæmorrhages may be seen here and there. The coats of the stomach are softened. It is often contracted, and it may be perforated, the aperture being irregular. If the acid escapes into the peritoneal cavity, it may act on almost any of the abdominal organs. Should the patient have lived long enough, there may be corrosion and inflammation of parts of the small intestine. The mucous membrane of the throat and larynx is inflamed and swollen.

Treatment. Alkalies should be given at once, *e.g.* soap and water, lime water, magnesia, washing soda ; and then demulcents, as milk, white of egg, oil, linseed tea. Do not use the stomach-tube if strong mineral acid has been taken, otherwise gently wash out the stomach. Morphine may be injected subcutaneously for the pain.

13. Acidum Mandelicum (B.P.). Mandelic acid $C_6H_5.CHOH.COOH$. *Synonym.* Phenylglycollic Acid.

CHARACTERS. A white crystalline powder. *Solubility*: 1 in 7 of water; 1 in 1 of 95 per cent. alcohol.

Dose, 30—60 gr. 2—4 G.

Action

Mandelic acid is absorbed rapidly from the alimentary tract and excreted unchanged in the urine. *In vitro* it is bacteriostatic in concentration of 1 per cent. at a *p*H of 5·7 and of 0·25 per cent. at a *p*H of 5. Large doses cause renal irritation and produce albuminuria.

Therapeutics

Rosenheim introduced mandelic acid for the treatment of urinary infections, *e.g.* **pyelitis** and **cystitis** especially if due to *Bacillus coli*, or to *Strep. faecalis*, in order to replace the effective but unpleasant ketogenic diet which acts by virtue of the excretion of β-hydroxybutyric acid. The results in uncomplicated cases are excellent. The drug may either be given as ammonium mandelate or as sodium mandelate. The latter is obtained in the following mixture :—

$$\text{Ac. Mandelic}\left\{\begin{array}{l}\text{grms. 3,}\\ \text{grs. 46}\end{array}\right. \text{Sod. bicarb.}\left\{\begin{array}{l}\text{grms. } 1{\cdot}6\text{,}\\ \text{grs. 23}\end{array}\right.$$

$$\text{Water to}\left\{\begin{array}{l}\text{mils 28}\\ \text{oz. 1}\end{array}\right.$$

An ounce of the mixture is taken four times daily. To assist in obtaining the necessary degree of urinary acidity for effective action, it is customary to prescribe also ammonium chloride 15 grs. in cachet four to eight times daily. The urine *p*H should be kept below 5·3. Improvement is seen in four to five days and the urine may be sterile in ten to twenty days.

Mandelic acid is contraindicated in severe renal disease with raised blood urea. It is seldom successful if obstruction to urinary flow is present. Acute febrile cases of pyelitis are best treated by other means until the pyrexia has settled.

Ammonii Mandelas. White, hygroscopic needles soluble in water.

Dose, 50 gr. 3·5 G. four times daily.

Ammonium mandelate has been used to replace the sodium salt and ammonium chloride. The NH_4 radicle is converted to urea whilst the mandelic acid fraction acidifies the urine.

Calcii Mandelas (B.P.). White, tasteless, insoluble powder.

Dose, 30—60 gr. 2—4 G. four times daily.

This drug has superseded the other preparations in the treatment of urinary infections. Though insoluble, it is split up by the gastric juices, even though free HCl be absent, and free mandelic acid is excreted in the urine, which is usually rendered sufficiently acid without the addition of ammonium chloride.

GROUP VII

Charcoal

Carbo (B.P.C.). Wood Charcoal.

SOURCE. Wood charred by exposure to red heat without access of air.

CHARACTERS. A black powder without odour or taste.

Dose, 60—120 gr. 4—8 G.

Carbo Activatus (B.P.C.). Activated Charcoal.

SOURCE. Charcoal prepared from vegetable matter is heated to a high temperature in a stream of activating gases, usually steam.

CHARACTERS. A fine black powder, 1 cubic inch of which offers an adsorbing surface of 20,000 square yards.

Action

External. Charcoal adsorbs gases including oxygen, and hence has an oxidizing power, parting with the adsorbed oxygen to oxidize organic and other substances. Organic matter is believed to be decomposed by aerobic micro-organisms which act by oxidation, and anaerobic which decompose directly, producing offensively smelling and toxic bodies. The **deodorant** action of charcoal is due to its converting anaerobic into aerobic decomposition. It adsorbs colouring matters, proteins and alkaloids. It has no direct effect on living organisms, and is not antiseptic.

Internal. Formerly it was thought only to oxidize when dry, but to a less degree it has this power when moist, presumably because there is still some active oxygen in its interstices. It is passed in the fæces unchanged.

Therapeutics

External. Charcoal has been recommended as a **deodorant** for foul ulcers, but it is a dirty preparation, and large quantities must be used. Activated charcoal is used in **gas masks** and effectively protects those exposed to noxious fumes as used in warfare. It is used as a purifying agent and decolorizer in various chemical processes.

Internal. It is used to adsorb gases in the gastro-intestinal tract, and thus it relieves **flatulence.** It is also used to tell the time of transit through the bowels. It has some power of adsorbing alkaloids and has thus been used as an antidote in cases of **opium** and **strychnine poisoning.** The action is neither complete nor lasting, and charcoal should thus be used as an expedient only until more effective measures can be taken. Its chief value in this connection is that it can be given after the stomach has been evacuated in the hope that it will adsorb that portion of the alkaloid which has already passed into the small gut.

GROUP VIII

Carbon Dioxide and Oxygen

CARBON DIOXIDE

Carbonei Dioxidum (B.P.) Contains not less than 99 per cent. of CO_2.

Action

External. In solid form it acts as a caustic. In solution the effect is of a mild rubefacient.

Internal. Carbon dioxide is readily absorbed in solution as carbonic acid from all mucous surfaces. It acts as a carminative in the stomach, and accelerates the absorption of water and alcohol. When administered by inhalation in pure form death results from asphyxia. In 5 per cent. concentration it acts as a powerful excitant of the respiratory centre, increasing the volume of air breathed per minute at least 500 per cent. In high concentrations this effect is followed by paralysis.

Therapeutics

External. The sudden release of liquid CO_2 from a cylinder produces a semi-solid snow, which can be formed into a stick or crayon. It can be moulded or cut with a knife to form a pencil which, covered to protect the hand, may be applied to nævi and warts. Its temperature is − 80° C. The pencil should be of such a size that when pressed down on the diseased part it covers the whole of it, if small, or a part 1 inch in diameter if large. The application is usually for about half a minute or a little longer.

Internal. A mixture of carbon dioxide, 7 per cent., in oxygen is inhaled to obtain the natural stimulating influence of carbon dioxide on the respiratory centre. It may be used also during the induction, or maintenance, of, or during recovery from, general anæsthesia. It is of great value if respiration is difficult in the new-born and also in the treatment of carbon monoxide and opium poisoning, asthma, resuscitation of the drowned, and pulmonary collapse.

Carbon dioxide is responsible for the effervescence of various table waters and certain wines and assists digestion by its carminative action.

OXYGEN

Oxygenium (B.P.) contains not less than 98 per cent. of O_2.

Action

Lack of oxygen raises the sensitivity of the respiratory centre to carbon dioxide. A rapid reduction of oxygen pressure causes marked hyperpnœa due to this increase of sensitivity. The result is that much CO_2 is washed out of the blood and, when its tension falls, a period of apnœa follows. If the lowering of oxygen pressure is a slow process, as in flying to a great height, the effect is more gradual and hyperpnœa is less evident. The flyer, however, is conscious of his deep respiratory movements. Slowly these give place to apnœa, because of the low CO_2 tension, even though cyanosis may be present as a result of anoxæmia. The power of judgment is lost, but the individual is quite unaware of it and unconsciousness supervenes with no previous distress.

Therapeutics

The logical use of oxygen is for conditions of anoxæmia, but it is not equally beneficial in all forms. The three types of anoxæmia are :—

1. *Anoxic.* Here the blood is inadequately oxygenated in the lungs and therefore its tension in arterial blood is low. Conditions which cause this are **asphyxia** as in drowning, high flying or mountaineering, diseases of the lungs interfering with gaseous exchange over a wide area, *e.g.* **pneumonia, massive collapse, pulmonary œdema** as caused by certain **poisonous gases,** and **poisoning** from **opium** and allied drugs.

2. *Anæmic.* In this type the hæmoglobin is deficient in quantity or is fixed, *e.g.* CO poisoning, anæmias, carboxyhæmoglobinæmia and meth- or sulphhæmoglobinæmia.

3. *Stagnant.* Here the blood is normally oxygenated in the lungs, but its supply to the tissues is inadequate. Examples are severe hæmorrhage, shock, and **heart failure.**

The greatest value of oxygen lies in its use for anoxic types of disease. In the anæmic and stagnant types the blood is nearly saturated with oxygen when it leaves the lungs, but an increase of its tension in the alveoli will result in more complete saturation and an increase of oxygen in solution. Even a slight increase may be of help, especially to the heart in stagnant anoxæmia. It is important to realize that venous unsaturation with oxygen which is normally 27 per cent. may rise to an unsaturation point of 40 per cent. before cyanosis is seen. Oxygen should, therefore, be given in pneumonia before cyanosis develops.

The maximum effect from the administration will be obtained by the use of an oxygen tent or a B.L.B. mask. When these are not available a stream of the gas should be passed through a double nasal catheter to the back of the nose. The use of a tube and funnel for oxygen inhalation is valueless. Two litres a minute must be given. The familiar practice of bubbling oxygen through water or brandy interposed between the cylinder and mask is quite futile for it yields one-fifth of a litre per minute.

GROUP IX

Iodides and other Iodine Compounds

1. Potassii Iodidum (B.P.) KI.

CHARACTERS. Colourless opaque crystals having a saline taste, without odour if pure. *Solubility*: 4 in 3 of water; 1 in 12 of alcohol (90 per cent.); 1 in 3 of glycerin.

Dose, 5—30 gr. 0·3—2 G.

2. Sodii Iodidum (B.P.). NaI.

CHARACTERS. A white, deliquescent, crystalline powder, with a saline taste. Freely soluble in water.

Dose, 5—30 gr. 0·3—2 G.

Action of Iodides

External. None.

Internal. The effect of iodides in the body is largely attributable to "salt-action": thus increase of bronchial secretion, and of urine output, is similar to that caused by other salts of the alkalies. On the other hand, iodine is undoubtedly set free to some extent in the body, for iodides may increase the iodine content of the thyroid gland, and free iodine may be found in the stomach and in organic combination in the hair. The deserved popularity of iodides as **expectorants** may be thus explained, the liberation of iodine acting as an adjuvant to "salt-action."

Absorption. Iodides are absorbed from the intestine very rapidly and appear in the secretions in ten minutes. They are distributed throughout the body, the smallest proportion being in the nervous tissues and fat, the largest in the blood. Some appears in the stomach as hydriodic acid.

Excretion. Eighty per cent. of the unchanged salt is excreted in the urine in twenty-four hours. It is also found in the saliva, sweat, and mucous secretions.

Iodism. When taken in excess, or even in small doses by susceptible persons, iodides produce a number of symptoms known as *iodism.* The patient complains of heavy pain over the frontal sinuses, running at the nose, sore throat, increased secretion of saliva, swelling of the salivary glands, and an eruption on the skin, consisting of acne, less commonly petechiæ, erythema, papules or bullæ. In rare cases there is albuminuria. The inflammation about the fauces may spread to the gums or down the trachea, setting up laryngitis, tracheitis, and bronchitis. Many patients complain bitterly of an unpleasant taste in the mouth and epigastric discomfort. These symptoms have been ascribed to an excessive formation of free iodine formed as mentioned above. The susceptibility to iodism varies very much. Reduction of dose will often abolish iodism, which may then not recur even if large quantities be again administered.

Therapeutics of Iodides

The most important use of iodides is for **tertiary syphilis** ; they cause absorption of gummata, possibly by inhibiting an antiferment which normally prevents enzymotic destruction of necrotic tissue. The pharmacopœial dose must, as a rule, be exceeded : patients sometimes take 150 to 200 grains a day. They are usually combined in treatment of **syphilis** with mercury or bismuth administration. In cases of aortic aneurysm their use should precede the employment of arsphenamines.

The use of iodine has superseded that of iodides in the treatment, conservative or pre-operative, of thyrotoxicosis. On the other hand, as a **prophylactic** of **goitre** iodine can best be given as potassium iodide mixed with common salt (1 : 100,000). If a person take 10 grms. of salt daily he would thus be supplied with 0·1 mg. of iodide, *i.e.* 0·076 mg. iodine.

Iodides are used as expectorants in chronic **bronchitis.** The secretion is rendered less viscid, partly on account of the specific effect, partly by virtue of salt-action.

IODOXYL

Iodoxylum (**B.P.**). *Tr. Names.* Pyelectan, Uroselectan B, Uropac. A pyridine derivative containing approximately 51 per cent. of iodine.

Characters. Greyish-white powder freely soluble in water.

Dose, 150—225 gr. 10—15 G.—by intravenous injection.

Preparation (**B.P.**)

Injectio Iodoxyli. Contains 0·75 G. (12 gr.) in 1 ml. (15 min.).

Dose, 150—225 gr. 10—15 G.

Action

The substance is in general non-toxic because no iodine is liberated, but, in susceptible persons, unpleasant reactions may set in immediately after the injection. These consist of a feeling of heat over the body, pallor, thready pulse, sweating and prostration. It is intensely irritating to the subcutaneous tissues. It is liable to produce phlebitis spreading from the point of injection into a vein.

Uses

It is used as a contrast medium and is introduced intravenously for purposes of X-ray of the urinary tract. As it is opaque to X-rays, the renal pelves, ureters and bladder can be seen in a radiogram.

Radiograms are taken five, fifteen, forty-five, and ninety minutes after injection.

Injectio Diodoni (**B.P.**). *Synonym.* Solution of Diodone. Diodone is a pyridine derivative. The Injection contains 17·5 per cent. of iodine.

Dose,	**300 min.**	**20 ml.** adult	intravenously.
	120—150 min.	**8—10 ml.** child	
	30— 45 min.	**2—3 ml.** infant	

Uses

A more stable iodine compound used for urography and arteriography.

IODIZED OIL

Oleum Iodisatum (**B.P.**). *Tr. Name.* Lipiodol.

Source. A combination of iodine and poppy seed oil.

Characters. An amber-yellow, oily fluid containing 40 per cent. by weight of iodine. It is opaque to X-rays.

Uses

The liquid is employed to render the bronchial tree, pathological sinuses, subarachnoid space and various other accessible cavities opaque to X-rays. In time it is coughed up from the lungs. In other situations it remains indefinitely and may give rise to irritation. This applies especially to intra-thecal introduction (4 mils), which may cause severe sacral pain subsequently. It should be removed after laminectomy. Iodism does not arise unless the fluid gains access to the stomach. 20–30 c.c. are employed to outline the ramifications of the bronchi, introduction being carried out by means of a cannula passed through the crico-thyroid membrane, or a rubber catheter passed *viâ* the nose through the vocal cords after preliminary cocainization. In the majority of cases the fluid will pass through the unanæsthetized larynx if allowed to trickle over the dorsum of the tongue, which must be pulled forwards during the process. Preliminary cocainization of the fauces and back of tongue should be practised.

IODOPHTHALEIN

Iodophthaleinum (B.P.). Disodium tetraiodophenolphthalein.

SOURCE. Prepared by the iodination of phenolphthalein. Contains not less than 85 per cent. of phthalein. The separated phthalein contains not less than 61 per cent., and not more than 62 per cent., of iodine.

CHARACTERS. A blue powder readily soluble in water, insoluble in alcohol. Opaque to X-rays.

Uses

Employed to give shadow of gall-bladder on X-ray films. The drug is excreted in the bile. It is usually taken by mouth after a light meal in the early evening. No more food is taken until the X-ray examination the next morning. After the first film is taken the patient is instructed to eat a meal containing plenty of fat. A further film is then taken to show the emptying capacity of the gall-bladder. The drug is very liable to cause vomiting or diarrhœa. In such cases a poor gall-bladder shadow must not be regarded as indicative of disease. When in doubt intravenous administration may be desirable. This is performed six hours before the X-ray examination.

Deaths have occurred soon after intravenous injection as the result of heart failure. The drug must be given in pure, freshly prepared and warmed 10 per cent. solution; the administration must be carried out slowly. A few fatalities have also been reported to follow some days after taking the drug by mouth. The cause was necrosis of the liver.

Dose, $\frac{1}{3}$—$\frac{1}{2}$ **gr.** per pound of body weight up to **75 gr.** **40—60 mg.** per kilo of body weight up to **5 G.**

Pheniodol. This is a contrast medium used for *cholecystography.* It is β-(4-hydroxy-3 : 5-diiodophenyl) α-phenyl propionic acid. It is insoluble in water and must be given by mouth only. Intravenous injection of the sodium salt causes convulsions due to action on the brain.

Dose, 3 G. for an adult of **10 stone.**
6 G. for an adult of **20 stone.**

This is the maximum.

The drug is given in a suspension and well diluted. It is taken at night and X-rays are taken the next morning. No food may be taken in the interval. It is vastly superior to iodophthalein in being less irritant to the stomach, in its absorption, and thus in the reliability of the radiograms.

GROUP X

BROMIDES

1. Potassii Bromidum (B.P.). KBr.

Characters. Colourless cubic crystals with saline taste. *Solubility:* 1 in 2 of water.

Dose, 5—20 gr. **0·3—1·2 G.**

Preparation **(B.P.)**

Tabellæ Potassii Bromidi. Contains 5 gr.—0·3 **G.** in each.

2. Sodii Bromidum (B.P.). NaBr.

Characters. A granular white powder in small cubic crystals with a saline taste. *Solubility:* 1 in about 2 of water.

Dose, 5—20 gr. **0·3—1·2 G.**

3. Ammonii Bromidum (B.P.C.). Ammonium Bromide. NH_4Br.

CHARACTERS. Small colourless cubic crystals with a pungent saline taste. *Solubility:* 1 in 1½ of water.

Dose, 5—30 gr. 0·3—2 G.

Action of Bromides

External. None.

Internal. *Alimentary canal.* The local action is that common to any salt. Thus concentrated solutions cause nausea and vomiting.

Nervous system. Bromides are powerful **depressants to the nervous system.** Thus, if an animal be given large doses, irritation of the cortical motor areas, which before easily excited movements, fails to do so. In man the higher functions of the brain are depressed before the lower, and these again before the spinal. Thus the depression takes place in regular order from above downwards, in the reverse order of the physiological development of the functions. Lassitude, depression and loss of memory are induced by large doses. The superficial reflexes are found to be depressed, or abolished, in particular that of retching following tickling of the pharynx. The drowsiness is accompanied by slowing of the respiration. Large and repeated doses induce some degree of anæsthesia of the body surface from central action.

Metabolism. The action is not specific but results from the general slowing of metabolism which accompanies lethargy.

Sexual organs. If bromides are taken for a long time, a failure of sexual vigour is produced, and ultimately there is a great lessening of the sexual appetite. Bromides are therefore anaphrodisiacs.

Absorption. Bromides are rapidly absorbed after administration, and are widely distributed throughout the body. In fact their behaviour, in this respect, is that of chlorides which they replace extensively, and the tissues are unable to distinguish between them. The greatest quantity is thus found in the blood and tissue fluids.

Excretion. Bromide is excreted by the stomach as hydrobromic acid which may give rise to indigestion.

At first the main excretion by the kidneys is rapid, but less than 20 per cent. is passed out in the first day. Thereafter the process becomes progressively slower, the kidneys removing bromide or chloride indiscriminately, so that elimination is not complete for six to eight weeks after a 60 gr. dose. Bromides thus present an outstanding example of **cumulative action.**

Bromism. If bromides are taken for too long a period, a series of symptoms of poisoning, to which the above name has been given, may appear. The commonest of them is a rash, consisting of red papules, chiefly on the face and back, resembling acne. The next symptoms are a general lowering of the cutaneous sensibility and also of that of the pharynx, then there is diminution of sexual power, the patient becomes low-spirited, easily fatigued, unfit for work, and his intellect is dulled, and in bad cases this passes on to dementia, melancholia, and other mental disorders. There may be a little conjunctivitis, and some increased secretion from the bronchi.

It is important to bear in mind that severe bromide intoxication may be present even in the absence of an acne eruption. The normal amount of bromide in the blood is 0·5 to 2·5 mg. per 100 c.c. The toxic threshold is in the region of 150 mg. per cent. in the elderly, or in those suffering from renal or cardiac failure; in the young adult the figure is raised to 200 mg. or more. Three hundred milligrammes may be regarded as an absolute threshold. Insomnia, delirium, confusion, hallucinations, hysterical manifestations, and torpor may occur at different times in the same patient and death directly attributable to the drug has been reported with a blood bromide of 500 mg. per cent.

The treatment is to give large quantities of normal saline solution by mouth, or in urgent cases intravenously.

Therapeutics of Bromides

External. None.

Internal. *Nervous system.* Because of their depressing effect bromides are used for many nervous diseases, especially **epilepsy**, acting no doubt by diminishing the excitability of the cerebral cortex. They rarely cure, but often greatly diminish the number of fits. The next most common use of bromides is as hypnotics. They are most useful when there is no organic cause to explain the **insomnia,** and therefore they are not employed when pain keeps the patient awake, but are given with great benefit in the insomnia of overwork, worry or that connected with the climacteric period. The sleep induced is quiet and refreshing, without dreams, and therefore these drugs are of value in nightmare, and in the night screaming of children. They act best in combination with chloral. Not only the insomnia, but the other nervous symptoms that are common at the **climacteric** period may be partially relieved by bromides. Various psychoneuroses derive some benefit from the exhibition of these drugs.

The have been used for **tetanus** and for **strychnine poisoning.** For the former they may be of some value in conjunction with the administration of avertin. For strychnine poisoning they must be useless if only on the grounds of the time factor involved.

The occurrence of acne may often be prevented by the simultaneous administration of arsenic.

Sexual functions. Because of their depressant effect bromides are given for spermatorrhœa and nymphomania.

Pyelography. Twenty-five per cent. sodium bromide is run into the renal pelvis through a ureteric catheter. As the solution is fairly opaque to X-rays, radiograms can thus be obtained.

Bromoformum (B.P.C.). $CHBr_3$.

CHARACTERS. A limpid, colourless, sweet liquid, soluble in alcohol, very slightly in water.

Dose, ½—2 min. 0·03—0·12 ml.

Action and Therapeutics

Bromoform has similar properties as a general anæsthetic to those of chloroform. Owing to its low volatility it cannot be used for this purpose. Prolonged administration may lead to fatty degeneration of the liver and to other toxic manifestations of chloroform poisoning.

It is used with trifling success in the treatment of whooping cough. It must be given in capsules or as an emulsion.

GROUP XI

Alcohols, Volatile Anæsthetics, and Nitrous Oxide

General cerebral depressants. These are commonly divided into three classes: Hypnotics or Soporifics, Narcotics, and Anæsthetics.

Hypnotics or Soporifics are drugs which produce sleep, closely resembling natural sleep.

They are used in the treatment of insomnia. The use of hypnotics is greatly abused. Those who take them become habituated to them, so that at last even large doses do not cause sleep. Chloral, the bromides, and the barbituric acid derivatives are the most satisfactory.

Narcotics are substances which produce abnormally deep sleep. Most hypnotics in excessive doses will do this. General anæsthetics are narcotics. It has been suggested that as many of these substances, *e.g.* chloroform, ether, sulphonal, methylsulphonal, chloral, and chloral formamide, are more soluble in lipoids than in water, they will accumulate in the nervous system, and thus exert their action. This may be so, but many hypnotics, *e.g.* bromides, are not specially soluble in lipoids, and many substances are soluble in them but are not hypnotics, so this question of solubility cannot be the whole explanation, although no doubt it is operative.

They are of great use in calming excitement and in ensuring deep sleep: opium and its derivatives are especially beneficial in relieving pain and thus producing sleep.

General Anæsthetics. These are drugs that lead to a total loss of consciousness, so that pain is no longer felt; at the same time reflex action is abolished. The higher and most recently acquired functions of the brain are depressed before those of more primitive origin. The resulting loss of inhibition produces evidence of extreme excitement which was wrongly held to indicate initial cerebral stimulation. As the depressant influence extends its sphere of action, so all power of movement and capability of sensation is lost.

The depression of the motor centres is followed by the depression of the muscular tone, and the muscles become quite flaccid and cease to respond to mechanical stimulation. This is the degree of narcosis that is required for the easy reduction of dislocations and for the manual examination of the abdominal viscera. Anæsthetics should not be pushed beyond this stage. If they are, even the involuntary muscles lose their tone and reflex excitability, so that the sphincters of the rectum and the bladder relax. The depression of the pulse and respiration continues, the movements of the chest become weaker and slower, the pulse becomes very feeble, slow, and irregular, and the heart finally stops in diastole. At any period of the administration during which recovery is possible, the functions of the body will return in just the reverse order to that in which they were lost. It is often many hours before the mental faculties have recovered their equilibrium, and long after the patient can move his muscles he cannot co-ordinate them. There are individual differences in the different anæsthetics and in different persons.

The general anæsthetics are—

(1) **Chloroform.**
(2) **Ether.**
(3) **Ethyl chloride.**
(4) **Vinyl ether.**
(5) **Nitrous oxide.**
(6) **Tribromoethyl alcohol**
(7) **Ethylene.**
(8) **Many other substitution products** derived from **alcohols and ethers.**
(9) **Barbiturates** designed for "basal narcosis."

The chief dangers of anæsthetics are—1. Early sudden death. This usually occurs before the patient is fully under the influence of the anæsthetic. Sudden heart failure ensues, possibly owing to abnormal inhibitory activity, but usually as the result of ventricular fibrillation. This is one of the greatest dangers of chloroform. Nervous patients are especially prone to sudden death in the first stage. This is due to the action of the excess of adrenaline which is liberated. This substance shortens the refractory period of the heart muscle and favours ventricular fibrillation. The preliminary use of basal narcotics greatly reduces the danger.

2. Death from paralysis of respiration. This is usually due to a combination of circumstances. Too much of the anæsthetic may have been given, respiration may be difficult because the patient suffers from some disease of the lungs, or the operation may demand that he should lie on his side or in some other position which hampers respiration. It is not a very great danger, for it is heralded by lividity; and if then the posture is changed, the administration of the anæsthetic is stopped and artificial respiration is performed, the patient usually quickly recovers; even if he does not, artificial respiration with the head thrown back and the tongue pulled out should be carried on as long as there is any evidence that the heart is beating, or if the patient draws a breath when artificial respiration is stopped for half a minute. Cases have recovered although it has been necessary to keep up artificial respiration for hours.

3. Cardiac failure may occur, owing to over-dosage acting directly on the heart, especially if the vapour is too concentrated. It is usually preceded, however, by signs of respiratory failure, provided that disease of the heart be not present. The length of interval between respiratory and cardiac stoppage varies inversely with the concentration of vapour inhaled. In such a case no more anæsthetic must be given, artificial respiration must be kept up in the manner just mentioned, and the heart may be stimulated by the plunging of electric needles into the heart, or even by opening the abdomen and compressing the heart through the diaphragm. The feet should be raised and the head depressed.

4. Vomited matter and, if the operation is about the mouth, blood may suffocate the patient. To avoid the first contingency no food should be taken for some time before the operation, and if the patient is sick he should be turned on his side; to avoid the second special precautions must be taken, which are described in books on operative surgery.

5. Reduction of body temperature due to depression of the heat-regulating centre. This is minimized by keeping the surroundings of the patient as warm as possible during the operation, and by the use of hot blankets and hot bottles afterwards.

6. Fatty changes in heart and liver and acidosis (chloroform), or bronchitis and pneumonia (chiefly ether).

For the relative advantages of the different anæsthetics and the mode of giving each, the account of the individual drugs must be consulted.

ETHYL ALCOHOL

Ethylic Alcohol. Ethyl hydroxide. C_2H_5OH

1. **Alcohol (95 per cent.) (B.P.).**

SOURCE. Distillation of fermented saccharine liquids.

CHARACTERS. Colourless, transparent liquid which burns with a blue, smokeless flame.

2. **Alcohol (90 per cent.) (B.P.).** Rectified Spirit. **Ethyl Hydroxide, 90** per cent. *by volume ;* **Water, 10** per cent.

3. **Alcohol (80 per cent.** *by volume*) **(B.P.).**
4. **Alcohol (70 per cent.** *by volume*) **(B.P.).**
5. **Alcohol (60 per cent.** *by volume*) **(B.P.).**
6. **Alcohol (50 per cent.** *by volume*) **(B.P.).**
7. **Alcohol (45 per cent.** *by volume*) **(B.P.).**
8. **Alcohol (25 per cent.** *by volume*) **(B.P.).**
9. **Alcohol (20 per cent.** *by volume*) **(B.P.).**

Action

External. Alcohol has an irritant action on skin and mucous membranes and to a greater extent on denuded areas. The effect is referable to precipitation of proteins particularly by strong solutions. It dissolves fat on the skin, and thus has useful cleansing properties, which may be useful preparatory to inunction of various remedies. Above a strength of 50 per cent., alcohol produces the usual signs of a rubefacient, whilst in lower strength it acts as a carminative. As an antiseptic it is comparable to a weak solution of phenol (3 per cent.), but only between concentrations of about 50 and 75 per cent. Absolute alcohol is very feeble in this respect because, in the absence of water, it cannot penetrate and destroy microbes.

Internal. *Mouth.* When concentrated, alcohol produces a feeling of warmth, or often even a **burning sensation,** in the mouth. If held there for some time the albumen of the superficial tissues is coagulated, and the mucous membrane becomes white, congested, and opaque, but this appearance soon disappears, as the coagulum is redissolved by the fluids of the tissues. Directly the alcohol is put in the mouth there is an increased flow of saliva and gastric secretion, and the pulse may be quickened; these results are reflex, but after absorption small amounts stimulate, large amounts depress the secretion of saliva. Alcohol has a slight local anæsthetic effect.

Stomach. Here also, if the alcohol is sufficiently concentrated, there is a sensation of warmth or even of burning. Neither vaso-dilatation nor coagulation is produced by even 70 per cent. alcohol in the stomach. This fact has been observed by the use of the gastroscope. If strong alcohol be taken repeatedly, however, gastric vaso-dilatation arises and is followed by excess mucus formation and even ecchymosis. In this way acute gastritis is produced and may pass into a chronic stage if the drug be continued.

Small doses, partly by virtue of the carminative effect, largely because they relieve anxiety and a sense of fatigue, and possibly because they assist absorption, aid digestion. These effects are enhanced by the bitters in beer and the ethereal esters in wines.

A single dose of alcohol introduced into the stomach in a concentrated form, *e.g.* neat brandy, immediately produces **important reflex effects.** The heart beats more rapidly and more forcibly, the vessels of the body dilate, especially those of the skin; hence there is a feeling of warmth. The blood pressure rises. These reflex effects are well seen in the immediate restoration of a fainting person by the ingestion of a single dose of brandy. Dilute alcohol, *e.g.* beer, does not produce them. They are quickly followed by the effects of alcohol upon the circulation due to its presence in the blood after absorption.

Intestines. Here alcohol has a slight **astringent** effect, and consequently it may check diarrhœa.

Liver. Alcohol has a destructive action on the hepatic cells, and even a single excessive indulgence may give rise to a transitory depression of liver function. Chronic alcoholism leads ultimately to the development of cirrhosis of the liver, but susceptibility to this disease varies enormously in different individuals. It is probably not entirely the direct result of the poison on the liver, but arises in part from the concomitant gastro-enteritis which allows of the absorption of toxic products of digestion and inflammation into the portal circulation.

Blood. It is absorbed quickly, from the stomach (20 per cent.) and small intestine (80 per cent.), none reaching the large gut. It appears in the blood in five minutes and reaches its maximum concentration in one and a half hours.

Symptoms of drunkenness appear when the concentration of alcohol in the blood reaches 0·15 per cent. In habitual drinkers a somewhat higher figure is required.

Temperature. Alcohol is **antipyretic**, lowering the temperature in fever, and with large doses in health. This is chiefly due to cutaneous vascular dilatation and rapidity of circulation, but also to depressing the heat-regulating centre.

Metabolism. 100 grammes of alcohol are chemically equivalent to 78 grammes of fat. It has been shown on fasting subjects that alcohol can arrest the increase of nitrogen excretion which accompanies inanition. It can in fact act as a food in replacing fat and effecting economy in protein usage. The general metabolism is unaffected except indirectly as the result of excitement, or of lethargy and coma. Uric acid excretion is increased, however, but this effect is not understood.

Excretion. Nearly all the alcohol ingested is oxidized in the tissues. After the taking of large quantities, from 5 to 10 per cent. may appear in the urine and expired air unchanged.

Circulation. The effects upon the circulation reflexly produced by stimulation of the mouth and stomach have already been mentioned. Alcohol has no direct stimulant effect upon heart or vaso-motor centre. The cutaneous vaso-motor system is almost always acted upon, the **vessels of the skin dilate**; therefore warmth and perspiration may be produced. Apart from a transient reflex elevation following the taking of strong alcohol the blood-pressure is unaffected or falls slightly as the result of vasodilatation. This effect will be offset should excitement and much activity supervene. Finally in alcoholic coma the blood-pressure falls.

Respiration. The rapidity of respiration and the amount of air breathed are very slightly increased by ordinary doses of alcohol, by reflex action. Very large doses depress the respiratory centre.

Skin. Alcohol is a **mild diaphoretic** on account of its vaso-dilator action. This gives a delusive sensation of warmth which leads to the taking of the drug before going out into the cold air. Heat loss will then be rapid, and where large doses have depressed the heat-regulating centre, the results may be serious.

Kidneys. Diseased kidneys are irritated even by the small quantities of alcohol which appear in the urine. It is a mild diuretic, and more pronounced effects are attributable to the volume of liquid ingested and to substances other than alcohol in the beverages.

Nervous system. The effect of alcohol on the nervous system is **depressant** to all its parts. In small doses it is thus beneficial, for the person who has taken it is not worried by trifles, and if shy is less self-critical, therefore feels more comfortable and may make an after-dinner speech with more confidence. The highest functions, including that of self-criticism, are first affected, and their depression leads to brilliant conversation and gaiety. If the dose has been large, the stage of depression of all functions quickly appears, proceeding regularly from the highest to the lowest. Thus the power of judgment is abolished very early by alcohol;

the emotions still remain vivid; but soon the subject loses all command over his emotions, cries and laughs irregularly, and loses control over his speech, talking incoherently and thickly; shortly afterwards he cannot talk at all, but can only make a noise. Muscular movements, which are not so highly developed as those of speech, are next affected; delicate, lately developed movements, such as writing, are for a time performed incoordinately. Next the grosser muscular movements are implicated, and the patient cannot undress himself or walk straight. Ultimately the activity of the reflex centres of the cord is abolished, the patient passes urine and fæces incontinently. The respiratory centre becomes paralysed and death ensues from respiratory failure. If alcoholic coma lasts longer than twelve hours, recovery is improbable. The depression of the reflex centres of the cord accounts for the fact that injuries which would kill a sober man may not kill a drunken one, for the heart and respiration, owing to the general central depression, are not affected reflexly by them. It must be remembered that with alcohol and drugs of similar action (*e.g.* chloroform) the apparent stimulation of nervous centres is really due to depression of inhibition, the aphrodisiac property is thus explained. Sexual power, as opposed to desire, is reduced.

Muscular system. Although alcohol is a food, its depressant effect on the nervous system is quickly seen in the depression of the power to do work, and although experiments on animals show at first a slight direct stimulation of muscular powers, and with some persons small doses perhaps at first stimulate the power of work, any action in this direction is slight, and is quickly followed by a depressant effect.

Therapeutics

External. Dilute solutions of alcohol have been applied to the skin of feverish patients, as they are cooling and refreshing. Stronger solutions (over 40 per cent.) are used to cleanse the skin or to harden it and protect it from **bedsores.** Ninety per cent. alcohol is injected into ganglia (*e.g.* Gasserian ganglion) or nerves (*e.g.* supra-orbital) in cases of **neuralgia.** Destruction of the nerve tissue by solution of lipoids and protein precipitation interrupts motor and sensory functions but seldom permanently (six to eighteen months). Alcohol is used as a solvent of phenol in cases of external or internal injury by this drug.

Internal. For reasons given, alcohol in moderation may be useful in aiding digestion. It is also useful because it increases the appetite, and it is a food which is absorbed without previous digestion. Owing to its anæsthetic property it may relieve vomiting, especially if taken with carbonic acid gas, as, for example, in the form of champagne or brandy and soda-water, and frequently, if concentrated, it will relieve flatulence. A single dose of strong spirits is often employed with great benefit for its reflex stimulant effects on the circulation for those who have fainted, or who are collapsed.

Strong alcohol relieves intestinal colic and checks diarrhœa.

For the various febrile diseases for which alcohol has been prescribed no specific action can be claimed. The indications for its use are the presence of anxiety and restlessness. The fact that the latter should be diminished seems paradoxical, but it must be remembered that the excitement of a drunken debauch is due to the effect of environment on an individual freed of inhibition by alcohol. A chronic alcoholic, if pyrexial, must not be deprived of the drug lest delirium tremens ensue.

Alcohol may, as just mentioned, be used as a soporific. Many sufferers from insomnia find that they sleep better for a glass of whisky and water at bedtime, because of its depressant action upon the highest centres, and this makes it of great use in any illness in which the patient is worried by trifles.

It aggravates epilepsy and also the headache due to arterial hypertension. Precordial pain, tachycardia and extrasystoles when referable to gastric flatulence respond well to small doses of strong alcohol.

It should not be given in the presence of inflammatory diseases of the urinary tract.

Toxicology

Chronic poisoning. Chronic gastritis, cirrhosis of the liver, gout, peripheral neuritis, and delirium tremens may all be attributable to excessive indulgence in alcohol, though not necessarily to the direct action of the drug on the structures involved. Thus the peripheral neuritis has been shown to be due to lack of intake of vitamin B_1 (because of poor appetite) and its poor absorption (because of gastro-enteritis). It renders patients particularly liable to phthisis, and makes them bad subjects for withstanding any severe illness, especially pneumonia. The increased tolerance of the heavy drinker is largely due to reduced absorption.

SPIRITUS METHYLATUS INDUSTRIALIS (B.P.)

Industrial Methylated Spirits

Source. A mixture of 19 volumes of alcohol (95 per cent.) with 1 volume of wood naphtha.

This substance may be used on the body surface or to disinfect instruments, but should not be taken internally.

N.B. It is a very indifferent antiseptic.

Alcohol Methylicum (**B.P.C.**). Methyl Alcohol. Wood Spirit. This is imperfectly oxidized in the body and poisonous substances are formed. Optic atrophy and death have both often happened as a result of drinking methyl alcohol.

Alcohol Benzylicum (**B.P.**) is an ingredient of the injection of ethanolamine.

Alcohol Cetostearylicum (**B.P.**) is an ingredient of Cera Emulsificans.

TRIBROMOETHYL ALCOHOL

Alcohol Tribromoethylicum (**B.P.**). CBr_3CH_2OH. Characters. Odourless white crystalline powder, unstable in air. *Solubility :* 1 in 33 of water ; freely in amylene hydrate.

Impurities. Heat, light and air favour decomposition with the formation of the irritating dibromacetaldehyde and hydrobromic acid.

Preparation (B.P.)

Bromethol. *Synonym.* Solution of Tribromoethyl Alcohol. *Tr. Name.* Avertin. A solution of tribromoethyl alcohol in amylene hydrate, 1 G. in 1 ml.

TEST FOR PURITY. Add 2 drops of 1 : 1000 Congo-red to 5 c.c. of avertin solution. A purple or blue colour denotes decomposition.

Dose, ½ to ⅔ min. per pound of body weight—0·075 to 0·1 ml. per kilo of body weight—by rectal injection.

Action

Absorption. When administered *per rectum* from 20 to 50 per cent. is absorbed in 20 minutes. The quicker the rate the stronger the narcotic action. The presence of hydrobromic acid will make the solution intensely irritating to the mucous membrane of the gut.

Concentration in Blood. 0·01 per cent. in blood produces full narcosis.

Fate in Body. It is broken down by the liver and combined with glycuronic acid to form urobromic acid. This process proceeds rapidly.

Excretion. As urobromic acid by the kidneys.

Heart. Diminution of force and rate of beat by direct action. Tribromoethyl alcohol is sixteen times safer than chloroform as regards cardiac effect.

Nervous system. Respiration slowed to 8 or 10 per minute. Overdosage produces apneusis, *i.e.* a cyclical irregularity consisting of several short expirations and inspirations preceded by a normal inspiration and followed by a normal expiration. Death occurs from respiratory failure. Anæsthesia commences within fifteen minutes of rectal administration and is soon fairly complete and associated with contracted pupils and muscular relaxation. There are no unpleasant after-effects, except possibly acute colitis. This does not arise if the solution has been correctly prepared and administered.

Therapeutics

An enema is given the night before the day of operation. Respiratory depressants, *e.g.* morphine, should be avoided because of the similar action of bromethol.

The amylene hydrate solution is mixed with water to produce a 2·5 per cent. preparation. This is warmed to slightly above body temperature and run from a vacuum flask into the rectum. In the majority of cases a little additional volatile anæsthetic is also required.

Contraindications

Inflammatory conditions of colon and rectum; severe renal and hepatic disease; hypothyroidism.

CHLOROFORM

Chloroformum (**B.P.**). Chloroform is Trichloromethane, $CHCl_3$, to which 2 per cent. of absolute alcohol has been added.

Characters. A colourless, volatile, heavy liquid, sp. gr. between 1·483 and 1·487, of a sweetish taste and a peculiar odour. *Solubility:* 1 in 200 of water, in which it sinks in heavy drops; 10 in 7 of alcohol (90 per cent.); freely in ether, olive oil, or turpentine.

Tests for Purity. (*a*) It must not redden blue litmus; (*b*) nor render cloudy silver nitrate; (*c*) nor give blue colour with cadmium iodide and starch; (*d*) nor turn yellow when agitated for one hour with H_2SO_4.

Dose, 1—5 min. 0·06—0·3 ml.

Preparations

1. **Aqua Chloroformi (B.P.).** Chloroform, dissolved in water, 0·25 per cent.

Dose, ½—1 fl. oz. 15—30 ml.

2. **Emulsio Chloroformi.** Chloroform, 5 per cent.; liquid extract of quillaia; mucilage of Tragacanth; water. Chloroform content is equivalent to that of Spirit Chloroformi.

Dose, 5—30 min. 0·3—2 ml.

3. **Spiritus Chloroformi (B.P.).** Chloroform; alcohol (90 per cent.), 5 per cent.

Dose, 5—30 min. 0·3—2 ml.

4. **Tinctura Chloroformi et Morphinæ Composita (B.P.C.).** Similar to chlorodyne. *Strength:* 1 millilitre contains chloroform, 0·075 mil; morphine hydrochloride, 0·01 grm.: acidum hydrocyanicum dilutum, 0·05 mil; tinct. cannabis, 0·1 mil. 10 ♏ contains chloroform, ¾ ♏; morphine hydrochloride, $\frac{1}{11}$ gr.; acidum hydrocyanicum dilutum, ½ ♏.

Dose, 5—15 min. 0·3—1 ml.

Action

External. Chloroform in many respects acts like alcohol, but it is more powerful. Thus if allowed to

evaporate on the skin it produces **cold**; therefore the vessels at the point of application contract, and at the same time **local anæsthesia** is induced. If the vapour be confined, or if chloroform be rubbed into the skin, it acts as an **irritant.** The vessels dilate, the part becomes red, and there is a sense of heat. This rubefacient effect may pass on to vesication. It is a powerful antiseptic and general protoplasmic poison.

Internal. *Mouth.* If concentrated, it produces irritation and a burning sensation. If dilute, it has a **sweetish taste,** which renders Aqua Chloroformi a valuable vehicle for the administration of nauseous drugs. It reflexly gives rise to an increased secretion of saliva, and is a local anæsthetic.

Stomach. The action of chloroform is like that of **alcohol.** Large doses cause gastro-intestinal irritation and vomiting, hence vomiting after anæsthesia, for when inhaled it is excreted into the stomach. Small doses produce a feeling of warmth, dilatation of the gastric vessels, an increased secretion of gastric juice, and more regular and more powerful gastric movements.

Absorption. It is absorbed into the blood from the stomach and intestines, and, if given as vapour, from the lungs. Ninety per cent. of it is combined with the cholesterin and lecithin of the red corpuscles, the remainder being free in the plasma.

Temperature. The temperature falls after the prolonged administration of chloroform, owing to depression of the heat-regulating centre. For this reason, it is essential that operating theatres should be kept warm.

Metabolism. After its administration the nitrogen and unoxidized sulphur in the urine are increased, indicating a greater destruction of protein and retarded oxidation. The blood sugar rises, and the liver is depleted of glycogen owing to a specific action on the liver cells. Diabetes is greatly aggravated by chloroform administration. Repeated inhalation of chloroform produces fatty degeneration, especially of the liver, heart, and kidneys. Albuminuria is common after chloroform anæsthesia.

Excretion. This takes place mainly by the lungs.

Nervous system. The phenomena resulting from the inhalation of chloroform are commonly divided into four stages.

First stage. This is at first one of depression of the highest functions. The imagination is momentarily unbridled, and the patient experiences a feeling of general warmth and comfort spreading over the entire body. The mind is confused. Roaring in the ears, extreme languor, and numbness of the extremities precede loss of consciousness. The power of hearing is maintained longer than that of the other special senses. In this stage the pupils are dilated and the pulse accelerated. At the same time that these higher functions are being depressed the lower motor functions are released from control.

Second stage. This is known as the stage of excitement, and may be completely absent. It is least marked in children or women and most evident in robust males and in drunkards. Apprehensive patients of either sex usually exhibit it to extreme degree. It is characterized by groaning, swearing, struggling and other evidence of excitement. The movements are usually directed in a semi-purposive manner to escaping from the anæsthetic, but consciousness is lost. The pulse is rapid, the respiration very irregular, and the pupils dilated.

Sudden death from ventricular fibrillation may occur in the first or second stage owing to the combined action of chloroform, vagal stimuli and adrenaline, the last two shorten the refractory period of the myocardium. Strangely this never occurs under light anæsthesia in a parturient woman.

Third stage. This is best called that of depression. It is important to remember that there is no sharp boundary line between the various stages; they pass insensibly into one another. In this stage the depression of the highest functions continues, so that the patient becomes completely unconscious, and he appears to be in a deep sleep. He sees, hears, and feels nothing; hence chloroform is called a general anæsthetic. The reflex centres are depressed, so that when the cornea is touched the eye does not shut. The pupil is contracted. The pulse and respirations become less frequent and less strong. The vaso-motor centre is depressed and the blood-pressure falls. The heart muscle is already depressed. As he cannot feel pain, and the reflex activity is so lowered that the heart will not be reflexly inhibited by the shock of an operation, this is the period at which to operate safely.

Fourth stage. In this there is a total abolition of reflex excitability. Even the lowest reflex centres of the cord are depressed, so that the patient may pass urine and fæces; all muscular tone is abolished, and consequently the muscles are quite flaccid. The pupil is widely dilated. If still more chloroform is given, the depression of the cardiac, respiratory, and vaso-motor centres continues, the pulse becomes feeble and irregular, and the heart finally stops in diastole owing to toxic action of chloroform on the heart muscle. The unstriped muscle of the arteries is also depressed, and they dilate. The respiratory movements become slight and irregular, with very long pauses between them. The blood pressure gradually falls to zero. In the early stages of anæsthesia death may occur from ventricular fibrillation. In the fourth stage over-dosage produces death by paralysis of the myocardium, the heart coming to rest in diastole. Poisoning of the respiratory centre results in arrest of breathing, and this event is followed by cardiac failure, the interval being inappreciable when high concentrations of vapour are employed.

In recovery from chloroform the lowest functions, such as muscular tone, are the first to reappear; but the patient does not regain his mental equilibrium for hours. Vomiting is common with return of consciousness and may persist for many hours.

Vomiting may also occur during the administration of chloroform, and its advent is often made known by pallor and wide dilatation of the previously contracted pupil.

Anæsthesia is produced by a blood concentration of

0·085 per cent.: death occurs at only double this concentration.

Therapeutics

External. Chloroform is employed in the form of a liniment to produce rubefacient and irritant effects in cases of chronic rheumatism, myalgia, and chronic inflammations. A drop of chloroform to the fluid ounce of urine or of animal and vegetable infusions or decoctions will keep them from decomposition.

Internal. It may be used as a local anæsthetic for toothache. It disguises the taste of nauseous medicines, and therefore Aqua Chloroformi is a very common vehicle, and Spiritus Chloroformi is much used as a flavouring agent. It may be given as the spirit for its carminative effect.

Inhalation. It is inhaled to produce anæsthesia for surgical purposes and parturition and also to relax spasm in tetanus and hydrophobia. Morphine to check excitement and atropine to prevent salivation and cardiac inhibition are injected before inhalation of chloroform.

The following points should be attended to in the administration of chloroform:

1. The respiration and pulse should be carefully watched for any signs of failure. The greatest care must be taken during the excitement stage, because a sudden gasp may load the blood with a dangerous concentration of the drug.

2. The operation should never be begun till reflex action is profoundly depressed—that is to say, till the stage of muscular relaxation has commenced. Many patients have been lost from neglect of this precaution, for the stimulus of the knife has reflexly stopped the heart, both vagal stimulation and adrenaline output increase favouring ventricular fibrillation. It is a common and dangerous error to think that, because the operation is trivial, it may be begun early; most of the deaths from chloroform have taken place early and when the operation has been slight.

3. Great care must be exercised if the heart be

fatty or feeble from any cause, or if the patient suffer from disease of the lungs, diabetes, or if he be very old.

4. In operations about the mouth care must be taken to see that no blood gets down the trachea.

5. It is desirable to have the stomach empty, therefore no solid food should be given for some hours before the administration. The patient's head must be so directed during vomiting that no vomited matters can get into the larynx.

6. False teeth should be taken out of the mouth.

7. The chloroform must be pure.

8. It should not be too concentrated. Two per cent. of chloroform is sufficient for induction, and 1 per cent. for maintenance of anæsthesia.

9. The head should be a little raised, and the lower jaw held up so that the tongue shall not fall back over the larynx.

10. Special care must be taken when the operation necessitates awkward positions, especially if respiration is interfered with, as in the lateral position used in obstetric and renal cases.

11. Because the temperature falls the patient should be kept warm.

If the pulse fails or the breathing becomes very weak, or stops altogether, artificial respiration should at once be commenced, the tongue being pulled forward by forceps to allow free entry of air to the lungs. The inhalation of carbon dioxide and the intravenous injection of lobeline stimulate the respiratory centre. The use of amyl nitrite is not only useless but dangerous. Adrenaline increases the liability to fibrillation under chloroform and is, therefore, contra-indicated. Artificial respiration should be maintained at least an hour or so, even if there is no sign of returning life; and if there is the slightest evidence of a cardiac beat, or a single automatic respiratory movement, it must be persevered in for even many hours. The heart has been restarted by opening the abdomen and compressing it through the diaphragm.

The use of chloroform is being rapidly superseded by less toxic anæsthetics.

Delayed Chloroform Poisoning. Occasionally repeated and very rarely a prolonged single administration leads to grave disorders of metabolism. The liver, heart and kidneys undergo fatty degeneration. The symptoms of acidosis are present. The danger may be minimized by the administration of 10 ozs. of glucose during the day prior to operation. Diabetes is made more severe by chloroform, which should not be used as an anæsthetic for sufferers from this disease. Sometimes, a few days after recovery from chloroform anæsthesia, the patient develops acute yellow atrophy of the liver with vomiting, fever, jaundice, often hæmatemesis and rapid shrinkage of the organ. The condition is fatal.

ETHER

Æther Solvens (B.P). $(C_2H_5)_2O$. *Synonym.* Ethyl Oxide.

Characters. A colourless, light, volatile liquid, with a hot taste and peculiar odour. It is very inflammable, boils between 34° and 36° C., and burns with a white flame. Sp. gr. 0·714 to 0·718. *Solubility:* 1 in 8·5 of water: freely miscible with alcohol and chloroform.

Preparation (B.P.)

Collodium Flexile.

Æther Anæstheticus (B.P.). *Synonym.* Ether.

Preparation (B.P.)

Spiritus Ætheris. Ether; alcohol (90 per cent.). Approx. 30 per cent.

Dose, 15—60 min. 1—4 ml.

Action

External. Ether evaporates very quickly, producing **great cold,** and consequently the part to which it has been applied becomes white from the contraction of the vessels. The cold is sufficient to cause such marked **local anæsthesia** that very slight operations may be performed upon the part anæsthetized. To produce this result ether is best applied as a fine spray. If it be rubbed in, or evaporation be prevented, it, like alcohol or chloroform, is an **irritant.**

Internal. In the mouth and stomach also it acts as a carminative. Directly it reaches the stomach it **reflexly** excites the heart, increasing the force and frequency of the pulse, and causing a rise of blood pressure. In the same way it excites respiration. It is quickly absorbed from the stomach or if inhaled from the lungs.

Nervous system. Ether is a powerful **general anæsthetic.** The phenomena and stages of ether anæsthesia are so like those of chloroform anæsthesia that the description already given will suffice. The following differences, however, should be noticed :

1. Anæsthesia occurs when the concentration of ether in the blood is 0·12 per cent. w/v. For chloroform the figure is 0·035 per cent.
2. Ether is much less dangerous than chloroform and has no appreciable effect on the heart.
3. Death from ether is due to paralysis of the respiratory centre and not to heart failure.
4. Ether is much more irritant to the respiratory mucous membrane, and hence is more liable to increase bronchitis in those already suffering from it.
5. With ether the stage of stimulation is more protracted, therefore there is more struggling.
6. For the same reason the anæsthetic stage is not reached so soon.
7. It is necessary to give at least four times the concentration of ether for induction of anæsthesia. This causes much coughing and laryngeal spasm.
8. Ether being very inflammable cannot be used in the close neighbourhood of a naked light.
9. With ether there is no risk of serious poisoning as with chloroform. Ether does, however, often produce ketonuria, albuminuria and casts. This suggests liver and kidney damage.
10. During ether anæsthesia the blood-pressure is raised.

Therapeutics

External. An ether spray is occasionally employed to produce local anæsthesia for small operations ; but as the ether makes the skin hard and brawny the operation must be quite superficial, and even then there is much subsequent tingling and pain.

Internal. *Stomach.* It has been used as a carminative in flatulent dyspepsia.

Heart. Administered subcutaneously (dose, 10 to 15 ♏, 0·6 to 1 mil) or by the mouth, ether acts as a reflex vaso-motor stimulant of value in fainting. Spirit of ether with an equal part of aromatic spirit of ammonia and some water forms an excellent restorative.

Inhalation. Ether is inhaled for the same purposes, and with the same precautions, as chloroform. It is unsuitable for purposes of induction because of the length of time and high concentration required to produce unconsciousness. Ethyl chloride, or a mixture of chloroform (2 parts) and ether (3 parts), should be used until the second stage is attained. Ether should not be given to patients suffering from bronchitis. Special works must be consulted for the employment, in combination, of chloroform, ether, nitrous oxide, oxygen and carbonic acid gas.

ETHYL CHLORIDE

Æthylis Chloridum (B.P.). C_2H_5Cl.

SOURCE. May be obtained by the action of hydrochloric acid on ethylic alcohol, or on industrial methylated spirit.

CHARACTERS. Gaseous at normal temperature and pressure, but as usually supplied is condensed into a colourless, mobile, inflammable, very volatile liquid.

Action and Therapeutics

This substance has a low boiling-point, and produces intense cold by its evaporation. It is sold in glass capsules terminating in a fine tube with a screw-capped point. When the capsule is held with the fine tube pointing towards the part to be anæsthetized, at about eight inches from it, the liquid ethyl chloride by its own vapour pressure is forced out as a fine jet, which impinges on the skin of the patient, and by its evaporation produces enough local anæsthesia for the performance of small operations, such as the removal of small warts. All fat must be removed from the skin by soap and washing with ether. It is given by the open method of inhalation for short operations or for the induction of anæsthesia to be maintained by ether. It is the most rapidly acting of all the volatile anæsthetics, unconsciousness being produced in half to one minute at a blood concentration of 0·03 per cent. Death occurs from heart failure.

VINYL ETHER

Æther Vinylicus (B.P.). *Tr. Name.* Vinesthene $(CH_2 \cdot CH)_2O$. A very volatile inflammable fluid with ethereal odour. Decomposes in air and light into formaldehyde and formic acid. It is supplied with the addition of 3·5 per cent. alcohol to reduce volatility and prevent freezing.

Uses

Vinyl ether is used to produce anæsthesia. It is given by inhalation and acts very rapidly with a high degree of potency. Death is produced by depression of the respiratory centre. The heart is unaffected by the drug. Central lobular necrosis of the liver. similar to that produced by chloroform, may occur.

ETHYLENE

Æthylenum (B.P.). $CH_2—CH_2$. *Synonym.* Olefiant Gas.

Source. Prepared by the action of orthophosphoric acid on alcohol (officially from the products of decomposition of petroleum).

Characters. An inflammable gas. When mixed with oxygen in certain concentrations it is explosive. It should contain not less than 98 per cent. by volume of ethylene.

Action

Ethylene, when inhaled in conjunction with 10 per cent. of oxygen, produces rapid loss of consciousness and surgical anæsthesia. This can then be maintained with concentrations as low as 80 per cent. This fact renders it superior to nitrous oxide, as the danger of asphyxia is absent. The respiration is somewhat shallow and rapid. The skin, metabolism and circulatory systems are unaffected. Vomiting occurs, however, in a third of those patients who have been subjected to prolonged administration.

Plants are very susceptible to the gas, 1 part in a million causing the leaves of leguminous plants to droop.

Uses

General anæsthesia.

TRICHLOROETHYLENE

Trichloroæthylenum (**B.P.**). $CHCl : CCl_2$. *Tr. Name.* Trilene.

CHARACTERS. Colourless liquid with odour of chloroform. Volatile but not inflammable.

Uses

General anæsthesia. It is used in industry for dry cleaning.

CYCLOPROPANE

Cyclopropanum (**B.P.**). $CH_2 : CH_2 : CH_2$.

CHARACTERS. An inflammable gas, explosive when mixed with oxygen. Contains not less than 99 per cent. C_3H_6.

Action

Cyclopropane produces unconsciousness rapidly when inhaled and a relaxation equal to that of chloroform. It is quickly eliminated, recovery of consciousness being reminiscent of that following nitrous oxide. The respiratory centre is strongly depressed; the blood pressure is raised. It is not irritating to the respiratory tract. It must be given with a high percentage of oxygen for 18 per cent. of cyclopropane will produce deep anæsthesia. This makes it valuable for major thoracic operations and in cases of cardiac disease. It is very costly, and must be administered, therefore, on a closed circuit with CO_2 absorption. Violent excitement may arise during recovery from prolonged anæsthesia.

Uses

General anæsthesia.

NITROUS OXIDE

Nitrogenii Monoxidum (**B.P.**). N_2O. *Unoff. Synonym.* Laughing Gas.

SOURCE. Prepared by heating ammonium nitrate.

CHARACTERS. A colourless gas, heavier than air; odour characteristic; taste, slightly sweet. Contains not less than 93 per cent. by volume of nitrous oxide. It is supplied in the liquid form in steel cylinders under a pressure of 50 atmospheres. It is not chemically allied to other anæsthetics, but is considered here for convenience.

Action

Outside the body it supports combustion because the heat is sufficient to split off oxygen. It is not of the same use to living tissues, and if it replaces oxygen it leads to asphyxia owing to the absence of oxygen.

Nervous system. When the gas is inhaled, the patient experiences, after a few seconds, a rushing noise in the ears, and indistinctness of vision. He feels he is losing control of his higher faculties; he may become uproarious if the concentration of gas is too low to produce unconsciousness; his speech and other movements are incoordinate: respiration becomes difficult, and by the time inhalation has lasted about thirty seconds he is cyanotic, and the following additional evidences of asphyxia are often present, viz., jerky, grunting stertor, muscular clonic twitchings, irregularity and finally stoppage of respiration. The face piece must be removed when cyanosis begins to appear, and it will be seen that there is no corneal reflex; the eyes are fixed, and the pupils dilated. The patient is also now completely anæsthetized, so that he does not feel a short operation, such as the withdrawal of a tooth. Muscular relaxation is not complete. Very soon after the removal of the face piece he takes a deep breath, and the lividity disappears. The stage of anæsthesia lasts from twenty to forty seconds, and after it the patient wakes in two or three minutes, and suffers from no after-effects.

It will be noticed that we have here the stage of excitation followed by depression. Whether the excitation is due to direct stimulation of the central nervous system or to removal of inhibition is undecided. The gas has a direct depressant action on the nervous system, but to procure this effect in full it has to be administered in such high concentration that asphyxia is very readily produced.

Circulation. Nitrous oxide has no direct influence on the heart. The rise of blood pressure and the slowness of the pulse are due to asphyxia. It is simply dissolved in the blood; the amount there corresponds to the partial pressure of the gas in the lungs.

Respiration. The asphyxia is chiefly due to deprivation of oxygen, for the gas replaces much of that in the blood. The glycosuria that occasionally occurs after its administration is due to the asphyxia.

Therapeutics

Pure nitrous oxide is used solely to produce anæsthesia for short operations. The steel cylinders in which the liquefied gas is contained have a tap which is worked by the administrator's foot. The liquid is vaporized directly it escapes from the cylinder, and it passes into a large indiarubber bag, from which the patient inhales it by a mask, with a valve so arranged that, while he can inspire from, he cannot expire into, the bag unless it be so wished. If oxygen is inhaled at the same time as the nitrous oxide, the direct depressant effects of the gas on the central nervous system can be produced without the asphyxial symptoms, therefore pure nitrous oxide is rarely employed, but various forms of apparatus, by means of which a mixture of oxygen (5 to 15 per cent.) and nitrous oxide can be administered, are used; by it patients can be kept anæsthetized for a long while without cyanosis.

The gas, 80 per cent., mixed with oxygen, 20 per cent., can be self-administered by a woman in labour. This will produce analgesia. The inhalation is begun as soon as each pain starts.

GROUP XII

Hypnotics

A large number of structurally dissimilar synthetic drugs comprise the pharmacological group of hypnotics. They are frequently referred to as hypnotics of the methane series in so far as they may be considered to be ultimately derivatives of this substance. For the same reason the term Aliphatic Narcotics or Hypnotics is alternatively employed as indicating the open-chain structure built up from methane by a series of simple steps. A convenient classification of these drugs is as follows :—

(1) **Halogen Derivatives.** Chloral hydrate, Butylchloral hydrate, Chloralamide, Chloralose, Chlorbutol (Chloretone).

(2) **Aldehydes.** Paraldehyde.

(3) **Sulphones.** Sulphonal (dimethyl sulphonal), Trional (methyl sulphonal), Tetronal (diethyl sulphonal).

(4) **Carbamates.** Urethane, Hedonal.

(5) **Urea Derivatives.** Barbitone, Phenobarbitone, Nembutal, Hexobarbitone, and various other barbiturates. Carbromalum is a **urea-halogen compound.**

(6) **Alcohols.** Amylene hydrate.

General Action of the Methane Hypnotics. In the main, the members of the various classes enumerated above have a similar action. This is characterized by depression of the sensory functions of the brain and the reflex activity of the cord. In this last respect and in their failure to exert any specific effect on pain sensation, they differ fundamentally from the narcotics of the opium series. Furthermore the respiratory centre is the last part of the central nervous system to become paralysed—a further differentiating feature and one which accounts for their comparative safety. The motor functions of the cerebral cortex are also depressed by the majority of these substances, but only to a slight extent by the urea derivatives.

Sufficient quantities of all these drugs will produce complete anæsthesia, but once this is established the action is dangerously prolonged, unconsciousness lasting for even three or four days. Many of the barbiturates are, however, free from this disadvantage, *e.g.* pentobarbitone, sodium amytal and hexobarbitone. The stages through which the patient passes, given an adequate dose, are (1) drowsiness with impairment of co-ordination; sleep occurs from which he can be easily awakened; (2) depression of reflexes but consciousness can be maintained; pain sensation is unimpaired; (3) loss of consciousness, limb reflexes and possibly the corneal reflex; depression of all sensation; (4) surgical anæsthesia with loss of corneal and tendon reflexes. The absence of a stage of excitement is largely attributable to the unexciting environment in which these drugs are usually taken. Paraldehyde has a peculiar tendency to produce motor excitability and even delirium in a feverish patient. Chloralose (glucochloral) differs from the other members by increasing the reflexes and even producing convulsions. Its action is more nearly related to that of morphine.

Individual differences between the behaviour of hypnotics will be mentioned under their respective headings.

CLASS I. **Halogen Derivatives**

Chloral Hydrate, Butyl-chloral Hydrate, Chloralamide, Chloralose, Chloretone

CHLORAL HYDRATE

Chloralis Hydras (**B.P.**). $CCl_3 \cdot CH(OH)_2$

SOURCE. Ethylic alcohol is saturated with dry chlorine, and thus chloral C_2Cl_3HO is formed. It is purified and water is added to form a hydrate.

CHARACTERS. Colourless monoclinic plates of a pungent, peculiar odour and a bitter taste. Easily melted by gentle heat. *Solubility:* Freely in water, alcohol (90 per cent.), and ether. All alkalies decompose it.

Dose, 5—30 gr. 0·3—2 G.

Preparation

Syrupus Chloralis (**B.P.C.**). Chloral hydrate, 1; distilled water, 1; syrup to produce, 5. *Strength:* 10 millilitres contain 2 grms. of chloral hydrate; 1 fl. dr. contains 10·9 grs.

Dose, 30—120 min. 2—8 ml.

Action

External. Locally applied it is irritant, causing vesication. In concentrated form it is disinfectant.

Internal. *Alimentary canal.* Unless well diluted, chloral hydrate is a gastric irritant; large doses may give rise to vomiting and purging.

Absorption. It is readily absorbed, and is taken up by the central nervous system in greater concentration than by any other tissue.

Excretion. In the body it is reduced to trichlorethyl alcohol, which combines with glycuronic acid to form urochloralic acid, in which form it is excreted in the urine. Some unchanged chloral is also excreted by this route and into the stomach.

Circulation. Therapeutic doses hardly affect this, but large ones **depress the heart** considerably, owing to local effect. The pulse, which may at first be slightly quickened, soon becomes slow, feeble, and irregular, and the heart finally stops in diastole. The **vaso-motor centre is depressed,** and consequently the vessels dilate. As a result of these actions on the heart and the vessels the **blood pressure falls,** but not to a greater degree than that produced by equivalent doses of other hypnotics.

Respiration. After large doses the respirations become slow and full, and after toxic doses they become irregular and shallow before finally ceasing. This is due to the action of chloral hydrate on the respiratory centre.

Temperature. Large doses cause a fall by diminishing the production and increasing the loss of heat.

Brain. Chloral hydrate is a **powerful hypnotic,** acting directly on the brain. Soon after taking a moderate dose the patient is overcome by sleep, which lasts several hours, and is indistinguishable from natural sleep. On waking there may be slight confusion and headache. Large doses produce coma. The pupil is contracted.

Spinal cord. The reflexes are depressed, and there is consequently paralysis and loss of reflex excitability.

Metabolism. Prolonged large doses lead to fatty degeneration of the tissues and to an increase of nitrogen, phosphorus, and sulphur in the urine, indicating an excessive breaking down of protein tissues. The urine reduces Fehling's solution ; this is due to the presence of urochloralic acid, not to sugar, as was formerly thought.

Therapeutics

Internal. Chloral hydrate is largely used for its hypnotic effect. Its great advantages over many other hypnotics are that doses sufficient to produce a deep sleep are not large enough to cause cardiac and respiratory depression, and the other harmful effects. Chloral hydrate is certain in its action; it quickly produces sleep; and there are no bad after-effects. Children take it well.

It is especially useful in simple insomnia from overwork or worry. Its disadvantages are that it does not relieve pain at all, and it should therefore not be used for insomnia due to this cause; it is also unsuitable for persons suffering from gastro-intestinal diseases because of its local irritant action. In febrile insomnia it is very valuable in the early stages, but must be given cautiously later when there is any danger of cardiac weakness. It does not relieve the distress and cough in diseases of the heart and lungs.

Toxicology

Acute Poisoning. As will be inferred from the action of chloral hydrate, the symptoms of poisoning by it are deep coma; a weak, feeble, irregular, slow pulse, which may become quick before death; diminished frequency of respiration and consequent lividity; and abolition of reflex movements. The surface of the skin is cold, and the temperature is subnormal.

Treatment. Give emetics or wash out the stomach. Keep up the temperature by hot bottles, hot blankets, friction, and massage. Prevent sleep by the injection of caffeine, shouting at the patient, hitting him, flapping with wet towels, bathing, &c. Give a subcutaneous injection of strychnine, because of its stimulant action on the cord.

Chronic poisoning. The taking of chloral hydrate is a vice to which some persons are addicted. A craving for it is soon established. The chief symptoms of chronic chloral poisoning are gastro-intestinal irritation, conjunctivitis, erythematous eruptions, dyspnœa dependent upon the cardiac and respiratory depression, and general weakness. There may be disturbance of the mental equilibrium, and persons have been known to become permanently weak-minded. A slightly larger dose than usual may be quickly fatal.

BUTYL-CHLORAL HYDRATE

Butylchloralis Hydras (B.P.C.). $C_4H_7Cl_3O_2$

Synonym Croton chloral hydrate. (This is a misnomer.)

SOURCE. Dry chlorine gas is passed through aldehyde. Butyl-chloral is formed. It is separated by fractional distillation, and water is added.

Characters. Pearly white crystalline scales, with a nauseous taste and a pungent odour like chloral hydrate. *Solubility:* 1 in 50 of water; freely in spirit and glycerin.

Incompatibles. All alkalies.

Dose, 5—20 gr. 0·3—1·2 G.

Action and Therapeutics

The action of this drug is exactly similar to that of chloral hydrate, but it is less certain in its effects. It is said to be less depressant to the heart, and to have a specific action in relieving neuralgia of the fifth nerve, but both statements are doubtful.

CHLORAL FORMAMIDE

Chloralformamidum (B.P.C.). $C_3H_4Cl_3NO_2$. *Synonym.* Chloralamide.

Source. Formed by the direct combination of formamide with anhydrous chloral. Should be preserved in amber-coloured bottles.

Characters. Shining colourless crystals. Taste slightly bitter. *Solubility:* Slowly in about 1 in 20 of water, 1 in 2 of alcohol (90 per cent.), and in weak acid solutions. Should not be heated over 140° F., or mixed with alkalies, for in either case it decomposes.

Dose, 15—45 gr. 1—3 G.

Action and Therapeutics

Chloralamide is similar in action to chloral into which it is decomposed in the body.

Glucochloral (B.P.C.). *Synonyms.* Chloralose, Anhydro-glucochloral.

Characters. Small white bitter crystals, slightly soluble in water.

Dose, 3—10 gr. 0·2—0·6 G.—in a cachet.

Action and Therapeutics

This drug is soporific, having a similar action to chloral, except that it produces increased reflexes and, in large doses, convulsions. It has but little effect upon the heart, and the respiratory centre is affected only by large doses.

Chlorbutol (B.P.). *Unoff. Synonym.* Chloretone.

Characters. White needles, sparingly soluble in water.

Dose, 5—20 gr. 0·3—1·2 G.—in a cachet.

Action and Therapeutics

It is a local anæsthetic, and 5 grains may be used, made into a suppository, for piles, and 1 part with 10 of zinc oxide forms a dusting powder for painful sores, as burns. Internally it is a good hypnotic, is useful for whooping-cough, and has been used successfully for sea-sickness. It is less toxic and irritating than chloral.

Class II. Aldehydes

PARALDEHYDE

Paraldehydum (B.P.). $C_6H_{12}O_3$

Source. A product of the polymerization of acetaldehyde.

Characters. A colourless liquid of ethereal odour and burning taste. Sp. gr. 0·998 to 1·000. *Solubility:* 1 in 10 of water; freely in alcohol and ether. It should be kept preserved from light and air.

Dose, 30—120 min. 2—8 ml.
½—1 fl. oz. 15—30 ml.—by rectal injection as a basal anæsthetic.

Action

External. It is antiseptic.

Internal. Large doses do not affect the gastro-intestinal tract, heart or metabolism; enormous doses kill by paralysis of the respiratory centre.

Nervous system. It is a **powerful hypnotic,** without any unpleasant after-effects, acting as a direct cerebral depressant. It operates quickly, and the sleep, which lasts several hours, is quiet, refreshing, and dreamless.

Therapeutics

It is given as an hypnotic in the same class of cases as chloral, and as it does not act on the heart it may also be used for patients suffering from cardiac disease. It has been used largely in asylums to produce quiet in **mania** and sleep in melancholia. It may produce an erythematous rash. Unless given in capsules the great objection to its use is its nasty taste, which is best covered by syrup and tincture of orange peel with at least two fluid ounces of water to ensure a usual dose being dissolved. It gives its unpleasant odour to the breath, which lasts many hours. Its nasty taste usually prevents the formation of a paraldehyde habit, but occasionally this is contracted and symptoms of delirium tremens may arise. Fatty degeneration of heart and liver have been reported. It has been used as a **pre-anæsthetic** hypnotic by rectal administration (0·5 mil per kilo body weight in an equal part of olive oil). It has been used in repeated doses in this way in the treatment of **tetanus.** In this disease it may also be given intramuscularly in 4 ml. doses.

CLASS III. **Sulphones**

SULPHONAL (B.P.)

Dimethyl-methane-diethylsulphone
$C_7H_{16}S_2O_4$

SOURCE. It is a product of the oxidation of mercaptol.

CHARACTERS. Colourless prismatic crystals, inodorous, almost tasteless. *Solubility:* 1 in 450 of cold, 1 in 15 of boiling water; 1 in 80 of alcohol (90 per cent.) or ether; 1 in 3 of chloroform.

Dose, 5—20 gr. 0·3—1·2 G.

Action and Therapeutics

Sulphonal is a direct cerebral depressant and **hypnotic.** It does not depress the heart. The drug is given for the same class of cases as chloral hydrate, but as it is so insoluble it is absorbed with difficulty and slowly; hence it takes three or more hours to act, its action may be prolonged into the next day, and it is unsuitable for frequent use. The symptoms of a sulphonal habit are general lethargy, mental, moral and muscular weakness, loss of nutrition, and dyspepsia. It and its congeners have a deleterious action on the liver with the production of fatty degeneration. It has been known to produce eruptions on the skin and hæmatoporphyrin in the urine. Sulphonal is excreted unchanged, but the process is a slow one and, therefore, cumulative poisoning may arise.

METHYLSULPHONAL

Methylsulphonal (B.P.C.). $C_8H_{18}S_2O_4$. *Unoff. Synonym.* Trional.

SOURCE. It is an oxidation product resulting from the condensation of ethyl-methyl-ketone with ethyl-mercaptan.

CHARACTERS. A white crystalline powder; slightly bitter. Almost insoluble in water and poorly in alcohol.

Dose, 5—20 gr. 0·3—1·2 G. Best given in cachet.

Action and Therapeutics

It is used for the same purposes as sulphonal, and like it may produce hæmatoporphyrinuria. As a rule it acts more quickly than sulphonal. A habit or disagreeable after-effects are rare, but the toxic symptoms are the same as those of sulphonal. It is a more powerful hypnotic and is broken down more easily by the body than is sulphonal. Cumulative action is thus rendered unlikely.

Tetronal (ethyl sulphonal), which contains two ethyl groups, is more powerful and more readily absorbed than the other sulphones. Women are much more susceptible than men to the action of this class.

Class IV. Carbamates

URETHANE

Urethanum (B.P.). Ethyl Carbamate. $NH_2 \cdot COOC_2H_5$.

Source. Interaction of ammonium nitrate and ethyl alcohol.

Characters. Colourless, inodorous crystals. *Solubility:* Freely in water and in alcohol.

Dose, 15—30 gr. 1—2 G.

Preparation **(B.P.)**

Injectio Quininae et Urethani (see *Quinine*).

Action and Therapeutics

A hypnotic of action similar to that of the whole group. It is rapidly absorbed and completely broken down in the body. Very large doses depress respiration but the toxicity is extremely low. It is possessed of growth-inhibiting qualities and has proved of great value in the treatment of **leukæmia**, especially the myeloid variety. Administration of 1 grm. thrice daily causes a striking fall in the white cell count in 3 to 4 weeks. It is the immature cells which are affected. A course-dosage of about 150 grms. is probably the optimum. A rise of hæmoglobin and red cells takes place as improvement in the leukæmic state is shown and the spleen undergoes a great reduction in size. Over-dosage may cause a dangerous fall of red and white cells. The response in lymphatic leukæmia is less good and more variable. It is used to aid the solution of quinine in the preparation of sclerosing liquids for injection into varicose veins.

Class V. Urea Derivatives

BARBITONE

Barbitonum (B.P.). $C_8H_{12}N_2O_3$. *Synonym.* Soluble barbital. *Tr. Name.* Veronal.

Source. May be obtained by the interaction of the diethylester of malonic acid, and carbamide.

CHARACTERS. A white crystalline powder. Inodorous. Taste, faintly bitter. Slightly soluble in cold water, more in hot and in alcohol, freely in aqueous alkaline solutions.

Dose, 5—10 gr. 0·3—0·6 G.

Preparation (**B.P.**)

Tabellæ Barbitoni. Contain 5 gr.—0·3 G. in each.

Barbitonum Sodium (B.P.). *Synonym.* Soluble barbital. *Unoff. Synonym.* Sodium barbitone. *Tr. Name.* Medinal.

SOURCE. Interaction of barbitone and sodium hydroxide.

CHARACTERS. A white, crystalline powder; bitter taste. *Solubility:* 1 in 6 of water.

Dose, 5—10 gr. 0·3—0·6 G.

Preparation (**B.P.**)

Tabellæ Barbitoni Sodii. Contain 5 gr.—0·3 G. in each.

Action and Therapeutics

This drug and its soluble sodium salt act as ideal hypnotics and in therapeutic doses have no further effect. Barbitone is absorbed readily but slowly excreted in unchanged form. It is therefore liable to give rise to cumulative poisoning characterized by erythematous rashes, cyanosis, incoherent speech and defective cerebration. Constipation, furred tongue and irritability are also common. Occasionally nystagmus can be elicited in these cases.

Women are more susceptible than men to this group of drugs. Owing to the slow excretion, barbitone should never be used in renal disease.

Acute fatal poisoning has followed the administration of 10 grs. of barbitone, but fatalities rarely occur with less than 50 grs. Death follows deep coma lasting for two to three days, and results from paralysis of the respiratory centre, or, more often, from a rapidly developed pneumonic consolidation with high temperature. The pupils are usually dilated. An addict to veronal may die as the result of a comparatively slight increase of his customary dose.

Modifications of Barbitone

The modified barbituric acids conform to the general formula $\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\!>\!\mathrm{B}$, where B stands for the barbituric nucleus and is constant, but the ethyl groups are replaceable by this, that, and the other. With every change in these ethyl groups a new barbiturate is born.

If a phenyl group C_6H_5 is used to replace one of the ethyl groups the drug seems to acquire special depressant power over the motor cortex. Such drugs can be used in epilepsy : luminal and prominal.

If sodium is added to the " B " nucleus without disturbing the essential ring formation the product becomes soluble. This confers greater speed in action—for example, barbitone sodium or medinal is far more soluble and quicker in action than simple barbitone or veronal. Solubility also makes it possible for one to inject the drug. Most of the basal anæsthetics are sodium compounds—for example, soneryl is a sleep-producer. Soneryl sodium, being more soluble, can be injected as a basal anæsthetic. Amytal sodium, evipan sodium, pernocton, and nembutal itself are all compounds of this class.

In the stage of intoxication which precedes narcosis susceptible patients show excitement. The preventive for such trouble is a preliminary dose of bromide. In certain cases, therefore, bromine has been introduced into the barbiturate nucleus—for example, noctal, pernocton.

Amidopyrine and Barbiturates

Attempts to confer pain-relieving qualities on the barbiturates have not been very successful. The closest approaches to a solution which have been made up to the present are the association of a barbiturate nucleus with amidopyrine in Pfeiffer's compound, used in veramon, and the linkage with a member of the morphine group in didial and codeonal. Amidopyrine, a derivative of antipyrine, is well known under the registered name of pyramidon, and appears to possess greater analgesic properties than antipyrine itself or other members of the simple coal-tar group. Its pain-relieving powers are enhanced by admixture with a simple hypnotic, possibly because the latter diminishes the patient's anticipation of pain.

Analgesics Based on Amidopyrine

Allonal =Amidopyrine + a barbiturate
Cibalgin = ,, + a barbiturate
Compral = ,, + a urethane
Veramon = ,, + barbitone

In each case pain relief is due to amidopyrine combined either mechanically or molecularly with a simple hypnotic. The danger of agranulocytosis developing in susceptible persons from even small doses of amidopyrine must be borne in mind. A barbitone derivative with pain-relieving qualities in its own right is still to be found.

PHENOBARBITONE

Phenyl-ethyl-barbituric acid

Phenobarbitonum (B.P.). *Synonym.* Phenobarbital. *Tr. Names.* Luminal; Gardenal.

CHARACTERS. White, odourless powder. Insoluble in cold water; soluble in alcohol.

Dose, ½—2 gr. 30—120 mg.

Preparation (**B.P.**)

Tabellæ Phenobarbitoni. Contain ½ gr.—0·03 grm. in each.

Phenobarbitonum Sodium (B.P.). *Synonym.* Soluble Phenobarbital *Tr. Names.* Luminal Sodium, Luminal Soluble.

CHARACTERS. The sodium salt of phenobarbital. Nitrate, hygroscopic powder, freely soluble in water.

Dose, ½—2 gr. 30—120 mg.

Preparations (**B.P.**)

1. **Tabellæ Phenobarbitoni Sodii.** Contain ½ gr.—0·03 G. in each.

2. **Injectio Phenobarbitoni Sodii.**

Dose, 1—3 gr. 60—200 mg. by intravenous or intramuscular injection.

Action

Phenobarbitone and its soluble salt are powerful hypnotics and have a special power of depressing cortical activity. Symptoms of idiosyncrasy are common and usually arise within two weeks of the commencement of administration. They consist of a morbilliform rash, especially on the forearms and legs, nystagmus, diplopia fever and vertigo. Both preparations are partly destroyed in the body; partly eliminated in the urine. They are not cumulative in therapeutic doses.

Therapeutics

These drugs are used extensively in the treatment of epilepsy. From ½ to 1 gr. repeated thrice daily is usually sufficient. If it is desired to combine them with bromides it is important to remember that soluble phenobarbitone is incompatible with ammonium salts. They are used also as hypnotics and in the relief of aural vertigo. Soluble phenobarbitone can be injected subcutaneously in 20 per cent. solution. Its chief value here is in the treatment of uræmic or of post-operative vomiting. The solution is apt to precipitate the insoluble compound on prolonged standing, or on boiling.

Phenytoinum Sodium (B.P.). *Synonym.* Soluble phenytoin. *Tr. Name.* Epanutin. It is sodium diphenylhydantoin.

Dose, ¾—1½ gr. 50—100 mg.

Action

This drug has a weaker narcotic action than that of barbitone or of phenobarbitone but is a strong anticonvulsant. Its action is depressant on the motor cortex. The toxic dose is close to the therapeutic dose and may cause gingival hypertrophy, dizziness, ataxia, diplopia, pyrexia, tremors, blurred vision, dermatitis, hallucinations, confusion, and muscular spasms.

Therapeutics

The drug is used in the treatment of epilepsy as an alternative to bromides or phenobarbitone. It is given in tablets or cachets 1½ grs. thrice daily rising if necessary to 3 grs. thrice daily. It is sometimes superior to these and has not the same tendency to cause drowsiness. It is the only drug used for epilepsy which will restore the epileptic encephalogram to normal.

Methylphenobarbitonum (B.P.). *Synonym.* Phemitone. *Tr. Name.* Prominal. Methyl-phenyl-ethyl-barbituric acid.

Dose, 1—3 gr. 60—200 mg.

Therapeutics

This barbiturate is used chiefly in the treatment of epilepsy and is probably superior to phenobarbitone in this respect.

Nirvanol. Phenyl-ethyl-hydantoin. White crystalline powder. Dose, 1½—5 gr. 0·1—0·3 G. in twenty-four hours.

Action and Therapeutics

The drug produces no obvious effect for several days: then drowsiness appears to be followed by the so-called "nirvanol sickness." This arises about one week after starting treatment, and consists of a morbilliform rash, pyrexia (up to 104° F.), conjunctivitis and eosinophilia. The clinical picture is remarkably like that of measles. Even the temperature follows the course of that disease, falling to normal with the disappearance of the rash in four days, provided that medication be discontinued.

The drug is used in the treatment of chorea. Improvement sets in with the occurrence of the reaction in less than half the cases treated. The drug is not without danger on account of its depressant action on the respiratory centre.

Dial. Diallyl barbituric acid.
Dose, 1½—3 gr. 0·1—0·2 G. Prepared as 1½ gr. tablets.

A valuable hypnotic of low toxicity. Particularly useful for the insomnia of mania.

Sodium Amytal. Sodium iso-amyl-ethyl-barbituric acid.
Dose, 3—9 gr. 0·2—0·6 G. Maximum 15 gr. Administered in solution (1 G. in 10 ml.) intravenously.

Action and Therapeutics

This drug is a powerful hypnotic and readily produces loss of consciousness and general anæsthesia. Administered intravenously, and less so orally or *per rectum*, it may cause a profound fall of blood pressure and respiratory weakness owing to action on the vasoconstrictor and respiratory centres. It is completely destroyed in the body, and none can be recovered from the urine even after intravenous administration. Drowsiness, yawning and sleep develop whilst the drug is actually being delivered into the blood stream. The action is less rapid, but safer, by other routes.

The advantage of its use as a pre-anæsthetic, or better, " basal narcotic," is that the patient is spared the unpleasantness of inhalation anæsthesia which is not started until consciousness has been lost. Furthermore, extensive operations can then be carried out under gas and oxygen, and there are rarely any unpleasant after-effects.

It is of great value in the treatment of strychnine poisoning, and should be given in full doses intravenously.

Sodium amytal should not be used in debilitated persons or those the subject of cardio-vascular disease. A marked fall of blood pressure during administration demands prompt cessation.

Pernocton. Sodium beta-bromallyl-barbituric acid.

Dose, average 5 gr. 0·3 G. Administered intravenously in 10 per cent. solution : 1 c.c. a minute until sleep comes on.

Action and Therapeutics

These are similar to those of sodium amytal. Pernocton has twice the hypnotic effect, produces no appreciable fall of blood pressure, and results in shorter anæsthesia and less excitement on recovery in comparison with amytal.

PENTOBARBITONE

Pentobarbitonum Sodium (B.P.). Sodium ethyl-butyl-barbituric acid. *Synonym.* Pentobarbital Sodium. *Tr. Name.* Nembutal.

Characters. A white crystalline powder ; soluble in water and alcohol.

Dose, 1½—3 gr. 0·1—0·2 G.

Action and Therapeutics

The action of pentobarbitone is similar to that of sodium amytal and less dangerous. If given as a basal narcotic it may be administered intravenously (7½ grs. in 10 c.c.) at the rate of 1 c.c. per minute. Injection should be stopped as the patient ceases to talk coherently and falls asleep. Pentobarbitone is often given by mouth in $1\frac{1}{2}$-gr. capsules. Two or three an hour before operation form a safe dose which can be advantageously combined with $\frac{1}{6}$ gr. morphine. Nine grains may be given in divided doses to produce amnesia and partial anæsthesia in labour. The effect is heightened if choral hydrate be also administered in 15 gr. doses hourly up to 60 grs.

It may also be used in strychnine poisoning (*q.v.*), and in tetanus.

HEXOBARBITONE

Hexobarbitonum (B.P.). *Synonym.* Hexobarbital. *Tr. Name.* Evipan.

CHARACTERS. A white crystalline powder sparingly soluble in water; readily soluble in hot alcohol.

Dose, 4—8 gr. 0·25—0·5 G.

A useful hypnotic producing a light refreshing sleep. It is rapidly destroyed in the body.

Hexobarbitonum Sodium (B.P.). The sodium salt of hexobarbitone. It is readily soluble in water.

Dose, 3—15 gr. 0·2—1 G.—by intravenous or intramuscular injection.
30—60 gr. 2—4 G.—by rectal injection.

Preparation (**B.P.**)

Injectio Hexobarbitoni Sodii.

Dose, 3—15 gr. 0·2—1 G.—freshly prepared.

Usually 1 grm. is dissolved immediately before use in 10 c.c. of distilled water. The solution is injected slowly (1 c.c. in 15 secs.), intravenously, whilst the patient is instructed to count aloud. The onset of unconsciousness is thus easily appreciated, and occurs after the administration of 3 to 5 c.c. About half as much again is given to produce deep anæsthesia with considerable muscular relaxation. Yawning, facial twitching and slight jactitation of the limbs may occur at the moment of loss of consciousness. The corneal reflex is lost, and the pupil slightly dilated. Respiration may be momentarily arrested if the solution be given too quickly. The action is remarkably evanescent, consciousness returning in ten to twenty minutes. The patient is then able to converse freely, but if left alone tends to fall into a natural sleep of short duration. There are no unpleasant after effects except occasionally excitement and restlessness. Opium preparations should not be given shortly before hexobarbitone, otherwise respiration may become feeble or arrested. A single intravenous dose of 1 grm. should never be exceeded.

Rectal administration is less rapid in its effect and more difficult to control. It is useful for children, or for adults whose veins are difficult to inject.

Hexobarbitone effectively controls the convulsions of leptazol, and reduces those due to strychnine and tetanus.

The drug is of great value for producing anæsthesia of short duration such as is needed for manipulative work or other minor surgery. Repeated small doses may be given to intensify gas and oxygen anæsthesia.

Kemithal. A thiobarbiturate whose sodium salt is administered intravenously to produce anæsthesia. It is half as potent as thiopentone and slightly less active than hexobarbitone. It is much safer than either for its therapeutic ratio is higher. The duration of action of equiactive doses is the same. Respiratory depression is less than that of thiopentone. About 5 per cent. is excreted in the urine, the rest is destroyed in the body.

THIOPENTONE

Thiopentonum Sodium (B.P.). *Tr. Name.* Pentothal.
Thiobarbiturate pentothal sodium. A yellow crystalline powder, soluble in water with the evolution of H_2S.

Dose, 1½—8 gr. 0·1—0·5 G.—by intravenous injection.

Preparation (**B.P.**)

Injectio Thiopentoni Sodii.
Dose, as above.

It is supplied and administered in the same way as soluble hexobarbitone. It is slightly superior to the latter in that twitching and jactitation seldom occur; on the other hand it is more depressant to the respiratory system.

A peculiar feature of the basal narcotics of the barbitone series is occasionally seen in the complete resistance of an individual to their anæsthetic effect even when administered intravenously. Thus 1 grm. may fail to cause even drowsiness. In some cases this must be attributed to an abnormally rapid breakdown of the drug in the body; in others this cannot be the case for the further administration of a grm. may result in sleep occurring promptly or an hour afterwards and persisting for twelve hours or more.

Carbromalum (B.P.C.). Bromo-diethyl-acetylurea. *Synonym.* Uradal. *Tr. Name.* Adalin. A white, crystalline powder.

Dose, 5—15 gr. 0·3—1 G.

A safe and pleasant hypnotic.

Toxicology of Barbiturates

Death following excessive dosage of any of the stable barbiturates is usually due to respiratory failure. This may occur in a few hours, but usually there is an interval of two or three days during which deep coma, small pupils, weak pulse, pale face, and subnormal temperature are followed by pyrexia and signs of extensive collapse of the posterior and lower portions of the lungs and hypostatic pneumonia. The pupils are moderately dilated terminally, and the facies dry and subcyanotic in colour. There is often a bilateral extensor plantar response.

Treatment. Sudden and dramatic recovery may occur after the intravenous administration of 5 c.c. of Injectio Nikethamidi. Picrotoxin may be injected hypodermically ($\frac{1}{6}$ gr.) but is a dangerous drug compared with the former.

Apart from this, the stomach should be washed out, and castor oil administered. The withdrawal of cerebrospinal fluid with its barbiturate content is claimed to do good, but the amount of drug removed must be minute.

Class VI. Alcohols

AMYLENE HYDRATE

Amyleni Hydras (B.P). $C_5H_{12}O$. *Synonym.* Tertiary Amyl Alcohol.

Source. From the interaction of amylene and sulphuric acid.

Characters. A colourless liquid of powerful odour resembling paraldehyde and camphor. *Solubility:* 1 in 8 of water.

Dose, 30—60 min. 2—4 ml.—in capsules.

Action and Therapeutics

The action of amylene hydrate is similar to that of paraldehyde, but twice as powerful. Its hypnotic effect is less than that of chloral. It first stimulates and then depresses the central nervous system, and produces a considerable fall of temperature. It is excreted largely through the lungs.

Apart from its use as a hypnotic, in which it may fail owing to the excitement induced, it is employed as a vehicle for tribromoethyl alcohol (*q.v.*). In such small quantity its stimulant effect may be exerted and thus protect to some extent the respiratory centre from depression.

(For description of other alcohols, see pp. 184–190.)

GROUP XIII

ACTION OF DRUGS ON THE NERVOUS SYSTEM

Many drugs which are derived from the vegetable kingdom owe their action to the presence of alkaloids, *e.g.* strychnine; a few to xanthines, *e.g.* caffeine in coffee; and in one instance to a phenolaldehyde, viz., cannabinol in Indian hemp. Drugs which stimulate the nervous system always produce subsequent depression or even paralysis if used in large quantities. Many alkaloids, particularly those which affect the brain, combine stimulant and depressant effects on different cerebral functions, or again, a function which is depressed in one individual may be exalted in another, *e.g.* effect of morphine on vomiting centre. Different levels of the nervous system are selected by different drugs for their maximum action, and the following classification is indicative of this tendency.

Action of Drugs on Nerve Endings

Nerve fibres are not affected directly by circulating poisons unless frequently introduced over a long period. In these circumstances lead and arsenic exert a direct effect on them.

Nerve endings are very susceptible to the action of certain drugs, but there is a great distinction here between somatic and splanchnic nerves, and between sensory and motor terminations. Thus, apart from aconitine and veratrine, the alkaloids have no effect on sensory nerve endings when introduced into the circulation. The action of local anæsthetics is produced by the high concentration in which they can be applied topically. Curara paralyses the motor nerve endings in voluntary muscle, nicotine and physostigmine stimulate the same point. Nicotine also stimulates and then depresses all the autonomic nerve ganglia. There is a selective action, however, of certain drugs in relation to the post-ganglionic nerve endings of the cranio-sacral and sympathetic systems. Thus atropine paralyses the former, though not exclusively, and adrenaline stimulates the latter. The innervation of the sweat glands forms an exception in both cases.

The term "nerve ending" is used here in the pharmacological sense and does not refer to an anatomical structure. This qualification is necessary because, although the action of the drugs to be discussed is exactly similar to that resulting from stimulation or paralysis of the nerves to the organs which they affect, yet it is in most instances unimpaired even after section and complete degeneration of the nerves. That the action is not exerted on the tissue of the organ is shown by the fact that activity arrested by the drug can be restored by direct stimulation of the specific tissue.

Dixon, and later Dale and Loewi have thrown much light on the ultimate mechanism whereby a nervous impulse results in a change in the organ to which it passes. It appears that the final stage is a chemical one: thus stimulating the para-sympathetic nerves, *e.g.* the vagus, causes the liberation of **acetylcholine.** This substance is inhibitory to heart muscle and explains, therefore, vagal slowing. It is probable that it is formed from a precursor compound by the arrival of the stimulus. Stimulation of the sympathetic fibres, on the other hand, results in the liberation of an adrenaline-like substance called "**sympathin**" which produces the same effects, *e.g.* acceleration of heart beat, as those of sympathetic activity. Nerves whose impulses are thus transmitted are termed **adrenergic.**

Atropine *paralyses* para-sympathetic nerve endings, not by preventing the formation of acetylcholine, but by preventing it from entering the receptive substance. Physostigmine imitates para-sympathetic stimulation and potentiates acetylcholine by preventing the naturally occurring hydrolyzing enzyme **choline esterase** from destroying it. At certain points, however, although atropine prevents the effect of injected acetylcholine, it does not prevent the effect of nerve stimulation. This is due to the impulses liberating acetylcholine so close to the cell that atropine cannot intervene. Sometimes the association is so close that atropine fails to prevent either effect. The nerves, whose effects are transmitted by acetylcholine, are termed **cholinergic** and these are divided into two groups according to whether their action resembles the effects of muscarine or of nicotine. Atropine prevents the effects of most of the former group, but has no action on the latter because here acetylcholine is liberated at ganglionic synapses or, in the case of skeletal muscles, at myo-neural junctions. The first, or muscarine-like, group affects constriction of the pupil, salivation, cardiac inhibition, bronchial constriction, increased tone of alimentary tract, bladder and uterus, and sweating.

The second, or nicotine-like group, affect all preganglionic fibres, the motor nerves to the skeletal muscles, and the nerves to the adrenal medulla. Thus all neurones leaving the central nervous system are cholinergic, and the only effector peripheral nerves that are not are the post-ganglionic fibres of the sympathetic nervous system, except those to the sweat glands and the vasodilators of muscle (Fraser).

Sympathin probably includes two substances :

(1) **Sympathin E**, which exerts the excitant action of adrenaline : (2) **Sympathin I,** which exerts its inhibitory effects. The former is produced by stimulation

of the cardiac sympathetic, for instance, whilst the latter is responsible for arrest of gut movement, or of bronchial spasm following upon sympathetic activity.

These facts should be borne in mind when meeting the term "myoneural junction" or "nerve-ending" in the following chapters. The words are retained for convenience.

Drugs acting on the Organs of Generation

A. Aphrodisiacs. These are substances which increase sexual desire or power. They may act by depressing inhibitory influences from the brain, or by stimulating the centres in the cord, or by causing congestion of the sexual organs. There are conceivably many ways in which this might take place.

The following drugs have been used as aphrodisiacs; their mode of action is discussed under their respective headings.

(1) **Strychnine.**
(2) **Cantharidin.**
(3) **Alcohol.**
(4) **Cannabis Indica.**
(5) **Yohimbene.**

B. Anaphrodisiacs. These are drugs having a depressant action on the central nervous system. The most important are:

(1) **Bromides.**
(2) **Antipyretics.**
(3) **Narcotics.**

Drugs acting chiefly on the Nervous System

The chief of these may be classified as follows:—

Class I. Acting on the cerebrum.

A. Cerebral depressants or soporifics:

Opium, and its Derivatives.
Hyoscine.
Cannabis Indica.

B. Cerebral excitants:

	Apomorphine.	
Deliriants	**Belladonna.**	Also act on nerve endings in glands and involuntary muscle.
	Stramonium.	
	Datura.	
	Hyoscyamus.	
	Cocaine.	
	Caffeine.	
	Theobromine.	

Class II. Acting also markedly on the spinal cord.
Nux Vomica, Yohimbene, Picrotoxin.
(**Bromides**, *q.v.*)

Class III. Acting on autonomic ganglia and nerve endings.
Conium, Gelsemium, Nicotine, Lobelia, Curare.
Cocaine, Cocaine Substitutes.
Aconite, Veratrine.
Pilocarpine, Muscarine, Physostigmine, Choline, Acetylcholine.
(also the **Belladonna** group).

Vegetable Drugs acting chiefly on the Cerebrum

Opium, Belladonna and Caffeine Groups

OPIUM

Opium (B.P.). The juice obtained by incision from the unripe capsules of *Papaver somniferum*, the white poppy, inspissated by spontaneous evaporation. It contains, when moist, not less than 9·5 *per cent. of anhydrous morphine.*

Characters. Rounded masses, coarsely granular, reddish or chestnut-brown, but becoming harder by keeping, and darkening to blackish-brown. Odour strong of poppy. Taste nauseously bitter.

Composition. (1) *Alkaloids.* At least eighteen in number, combined with meconic, lactic, and sulphuric acids. The following are the important alkaloids existing in opium :—

Phenanthrene Derivatives	*Benzylisoquinoline Derivatives*
Morphine 10 per cent.	Narcotine 6 per cent.
Codeine 0·5 per cent.	Papaverine 1 per cent.
Thebaine 0·2 per cent.	Narceine 0·3 per cent.

(2) *Neutral body.* Meconin.

(3) *Organic acids.* Two in number :
Meconic acid. Lactic acid.

(4) *Water*, 16 *per cent.*

(5) *Mucilage, resin, albumen, glucose, fats, essential oil, caoutchouc, odorous substances, and salts of ammonium, calcium, and magnesium.*

N.B. When Opium is prescribed, Opium Pulveratum shall be dispensed.

Opium Pulveratum (B.P.). Powdered Opium. *Synonym.* Pulvis Opii.

Source. Opium dried at a moderate temperature and powdered. It is adjusted if necessary by the addition of lactose to contain 10 per cent. of morphine (anhydrous).

Characters. Light brown powder with odour of poppy.

Dose, ½—3 gr. 30—200 mg.

Preparations (**B.P.**)

1. Pulvis Cretæ Aromaticus cum Opio. Powdered opium; aromatic chalk powder. *Strength of opium*, approx. 1 in 40.

Dose, 10—60 gr. 0·6—4 G.

2. Pulvis Ipecacuanhæ et Opii. *Synonym.* Dover's powder. Powdered opium; ipecacuanha; lactose. *Ten per cent. each of opium and ipecacuanha.*

Dose, 5—10 gr. 0·3—0·6 G.

(Tabellæ Ipecacuanhæ et Opii. 5 gr. in each.)

3. Tinctura Opii. *Synonym.* Laudanum. Sliced opium; alcohol (90 per cent.), and water, q.s. *Standardized to contain* 1·0 *per cent. of anhydrous morphine.* That is 1 grm. in 100 millilitres or 1 gr. in 110 ♏.

Dose, 5—30 min. 0·3—2 ml.

4. Tinctura Opii Camphorata. *Synonym.* Paregoric. Tincture of opium, 50; benzoic acid; camphor, 3; oil of anise; alcohol to make 1000. *Strength:* Contains 5 milligrms. morphine in 10 millilitres (0·05 per cent.) or $\frac{1}{37}$ gr. in 1 fl. dr.

Dose, 30—60 min. 2—4 ml.

Morphinæ Hydrochloridum (B.P.). Morphine Hydrochloride. $C_{17}H_{19}O_3N,HCl,3H_2O$.

Characters. White cubical crystals. *Solubility:* 1 in 25 of water; 1 in 50 of alcohol (90 per cent.); 1 in 8 of glycerin.

Dose, ⅛—⅓ gr. 0·008—0·02 G.

Preparations

1. Liquor Morphinæ Hydrochloridi (B.P.). Morphine Hydrochloride, 1; dilute hydrochloric acid, 2; alcohol (90 per cent.), 25; water, to make 100. *Strength:* 1 per cent. or 1 gr. in 110 ♏, 1 grm. in 100 millilitres, or about 4½ grs. of the hydrochloride to 1 fl. oz.

Dose, 5—30 min. 0·3—2 ml.

2. Suppositorium Morphinæ (B.P.). Morphine Hydrochloride, 0·015 G. (¼ gr.).

3. Tinctura Chloroformi et Morphinæ Composita (B.P.C.). *Strength.* $\frac{1}{11}$ gr. in 10 ♏.

Dose, 5—15 min. 0·3—1 ml.

4. Trochiscus Morphinæ et Ipecacuanha (B.P.). Morphine Hydrochloride, 2 G.; ipecacuanha, 6 G. for 1000 lozenges. *Strength:* 0·002 G. of morphine hydrochloride or $\frac{1}{32}$ gr. in each: 0·006 G. or $\frac{1}{10}$ gr. ipecacuanha.

Morphine Sulphas (B.P.). Morphine sulphate. $(C_{17}H_{19}O_3N)_2, H_2SO_4, 5H_2O$.

CHARACTERS. White crystals. *Solubility :* 1 in 15·5 of water.

Dose, $\frac{1}{8}$—$\frac{1}{3}$ gr. 8—20 mg.

Preparations (**B.P.**)

1. Injectio Morphinæ Sulphatis.

Dose, $\frac{1}{8}$—$\frac{1}{3}$ gr. 8—20 mg.

2. Injectio Morphinæ et Atropinæ. Contains 0·06 per cent. atropine sulphate ; 1 per cent. morphine sulphate.

Dose, 8—15 min. 0·5—1 ml.

Action

The action and uses of opium in man are due almost entirely to its morphine, and therefore they may be studied together. It should be noted that papaverine causes relaxation, thebaine contraction, of plain muscle. Stimulation of the cord is most marked by thebaine which will give rise to strychnine-like convulsions. The amount present in opium is too small to produce any effect.

External. Opium has no action when applied to the unbroken skin, or to mucous membranes.

Internal. *Alimentary canal.* As far as we know opium diminishes all the secretions of the body except the sweat. The mouth consequently becomes dry. In the stomach and intestine the secretion of the gastric and intestinal juices is diminished. Opium produces increase of gastric tone especially in the pyloric antrum, often spastic contraction of the pylorus and inhibition of normal peristalsis in the stomach. Its emptying is delayed. The delay in the passage of food following morphine administration is largely referable to spasm of the pyloric and ileo-colic sphincters. Increased small gut peristalsis and increased colonic tone tend to counteract this effect. They do not occur after opium because of the other alkaloids, notably papaverine. Opium is, therefore, more constipating than morphine. The action is on the nervous or muscular structures in the wall of the intestine itself, and is quite independent of the central nervous system.

Opium appeases hunger, almost always gives rise to **constipation,** and in some persons causes **vomiting,** often most marked many hours after the drug has been taken. This action is due to the effect of morphine on the vomiting centre which is sometimes stimulated. It is more likely to arise after the administration of morphine than of opium.

Butsch, McGowan and Walters have investigated the effect of morphine on intrabiliary pressure. The experiments were performed on patients whose common bile ducts were being drained. One-sixth grain of morphine injected subcutaneously causes a rise of intrabiliary pressure from a normal of 0 to 20 mm. to 200 to 300 mm. of water. This is associated with epigastric discomfort or even biliary colic. The rise in duct pressure is due to constriction of its lower end. The spasm is relieved by amyl nitrite and unaffected by atropine and hyoscine.

Excretion. Morphine is excreted to a slight extent by the kidneys. Most of it is excreted in the fæces. Some is excreted in the milk and may affect the child.

Fate in Body. Morphine for the most part circulates in the blood as such. A third of it is destroyed in the body, probably in the liver ; if morphine is taken habitually, the amount so destroyed gradually increases, but not proportionately with the increase of dose. A considerable quantity is stored in the skeletal muscles and slowly liberated. Tolerance is acquired quickly and to an enormous extent if morphine be administered even only once a day. It is to be explained, however, on the great increase of urinary excretion and the enhanced resistance of the brain to the drug's action, and this explains why some persons can take such large quantities.

Circulation. Some slowing of the heart occurs from stimulation of the vagal centre. The heart is not directly affected by morphine. The slowing of rate and rise of blood pressure seen after full doses is due to asphyxia.

The vaso-motor centres are slightly depressed by moderate doses, hence the **vessels,** particularly those of **the skin, dilate**; with large doses the depression is considerable.

Nervous System. Medullary Centres. Morphine has a selective action on the respiratory centre, which it depresses. The actual rhythm is retarded and, although the centre is still subject to the influence of reflex and chemical stimulation, it can only respond by increase of depth of breathing. Breathing therefore becomes slow, though deepened. Cheyne-Stokes' respiration often precedes death, which takes place from **asphyxia.** The cough centre is depressed. The vagal centre is stimulated and thus causes slowing of the heart. Vomiting is due to stimulation of the vomiting centre.

Cerebrum. In a few people the higher faculties are at first slightly excited by small doses with but little inco-ordination. The intellectual power and mental vigour appear increased, and the drug is taken by some to enable them to do their mental work. The power of continuous attention is depressed, however. Usually the excitation does not affect the mind evenly; generally the imagination is powerfully and pleasantly excited, much more so than the faculties of reason and judgment, which are a little dulled. The expression on the face is one of happiness and comfort, and this corresponds with the condition of mind, which is in a state of peace, calm, and happiness. This is soon succeeded by sleep, which is accompanied by pleasant dreams. Large doses produce deep coma, complete insensibility, periodic breathing and anoxæmia. Morphine has a selectively depressant action on the sensation of pain and the respiratory centre, both effects being observed whilst the intelligence is still unimpaired. On waking from sleep induced by opium some persons feel quite well, but usually there is languor, headache, and nausea. If a large or even moderate amount is given, generally there is no primary excitement, and then the first symptom that opium has been taken is drowsiness. The **pupils contracted**; this is due to stimulation by the drug of the oculo-motor centre. Before death, the pupil dilates owing to asphyxia. The cerebral motor centres are depressed and their excitability eventually abolished. Vomiting is occasionally caused by transient stimulation of the vomiting centre, but soon this is depressed, and therefore emetics do not act well in cases of opium poisoning.

Spinal Cord. The reflex irritability of the spinal cord is greatly increased in animals. In man it is usually depressed, but relatively little in comparison with the effect on the brain.

The excitability of motor and sensory nerves is unaltered except that in the later stages of opium poisoning by enormous doses it is depressed, that of the sensory before the motor. The muscles remain irritable to the last.

In **frogs** morphine produces violent convulsions, because its predominating action is to stimulate the spinal cord. **Birds** are only affected by large doses, which produce coma. **Mammals** are for the most part affected in the same way as man, except that the first or excitement stage is more marked ; hence with many mammals, especially cats, morphine is a violent convulsant ; dogs and rabbits require large doses to produce symptoms.

Kidneys. Opium has no direct effect on the urinary flow.

Skin. Opium is a mild **diaphoretic.** It may cause itching.

Metabolism. If opium be given to a diabetic, the amount of sugar he passes in the urine is frequently diminished. The reverse effect is seen after doses sufficient to produce partial asphyxia and the glycogen stores of the body are depleted. General metabolism is slightly decreased also, for the amounts of nitrogen and carbonic acid excreted and oxygen absorbed are lessened. The temperature is lowered by large doses.

Therapeutics

External. The topical application of opium in the form of liniments and ointments is based on the fallacious assumption that it exerts an action on the peripheral nerve endings. This is not the case except in dangerous concentration. The use of the opium suppository is favoured because slow absorption over a long period is produced. The analgesic action is a central one and therefore there is no reason why this form of medication should be reserved for rectal and anal diseases.

Internal. *Digestive system.* Opium may be given half an hour before the exhibition of a drug which is liable to cause vomiting unless thus hindered from doing so. It was used in this way when ipecacuanha was given for dysentery. It may be of similar help in preventing the vomiting of sulphapyridine. Opium is invaluable for checking **diarrhœa.** Intestinal colic is generally relieved by opium. It is very effective in lead colic. If in acute inflammatory conditions of the peritoneum, as appendicitis, no operation is possible, full doses of opium must be given, the object being so to paralyse the intestinal movements in order to prevent spread of the infection.

Cardio-vascular system. In **congestive heart failure** opium or morphine is of great value. The shallow rapid respirations give place to slower deeper breathing with certainly no impairment of ventilation. The anxiety and restlessness are allayed and the patient often sleeps well when no other soporific has been of any avail. It is a fallacy to regard the cyanosis of heart failure as a contraindication to the use of opium. In severe heart failure it is wise to give morphine by injection because absorption from the intestinal tract is erratic. As improvement occurs papaveretum by mouth may be substituted for morphine which is more likely to cause vomiting.

In the **left ventricular failure** of chronic hypertension opium or morphine may be life-saving. Papaveretum gr. ½ by mouth nightly seems to act as a specific in preventing cardiac asthma.

Morphine should be injected to control **hypertensive encephalopathy.**

In cases of **hæmorrhage** opium is a good indirect hæmostatic, as in general it reduces voluntary and involuntary movement. It is particularly valuable in the treatment of intestinal hæmorrhage, hæmatemesis and hæmoptysis.

Respiratory system. It will be remembered that opium depresses the respiratory centre; therefore it, by diminishing the activity of the centre for the reflex act of coughing, will often alleviate this distressing symptom, but it is only justifiable to give it when the irritation which reflexly sets up a cough is irremovable, as in intra-thoracic growth or aneurysm, or when there is little or no lividity and yet the cough is violent, as is often the case in simple catarrhal tracheitis, pleurisy, and to a less extent in phthisis. The liability to cyanosis in many diseases attended with cough must never be forgotten, but except in the very feeble it is not a contraindication to its use if oxygen be administered continuously. Thus opium is quite inadmissible in the last stages of bronchitis and pneumonia. Death is very apt to follow the use of opium or heroin in the asthenic bronchitis of the aged. Cyanosis and œdema of the lungs may be induced by a single dose.

In pneumonia it is very useful, lessening cough and pain and promoting sleep. Opium must not be given for asthma, as there is in this disease a great liability to the growth of a permanent opium habit.

The combination of opium with ipecacuanha in the form of Dover's powder is advised for a dry, useless cough. The former depresses the cough reflex, the latter may act as an expectorant, thus soothing the inflamed surfaces. It is liable, however, to cause nausea or even vomiting.

Pain. Opium and morphine are used pre-eminently for the relief of pain. It follows that these drugs are often employed in the most diverse conditions. Owing to the selective action in blunting this sensation, comparatively small doses are often adequate. On the other hand, tolerance is so soon developed, and to such a high degree, that great caution should be exercised in the use of morphine. It is indicated for acute pain of which the cause will probably yield to treatment, and again in painful but incurable diseases where milder analgesics fail to produce relief. As a general rule, members of the antipyretic group should be tried first, for addiction to their use is attended by less serious consequences. When pain is due to colic the benefit of morphine is much enhanced by the simultaneous administration of atropine.

Insomnia. The value of the drug in the sleeplessness of heart disease has been referred to. For insomnia due to pain, opium is again indicated. It should not be used for the restlessness of mania which it may aggravate. Hyoscine is here the drug of choice. For chronic insomnia, opium and its derivatives should never be employed.

Anæsthesia. Morphine is often used to allay nervousness and to aid the action of the subsequently administered volatile and gaseous anæsthetics. Its use for this purpose is being superseded by that of the basal narcotics. As a pre-anæsthetic injection it should be combined with atropine to diminish bronchial secretion. In conjunction with scopolamine it is used for the production of "twilight sleep" in labour.

Diaphoresis. Opium is often used for this purpose in conjunction with ipecacuanha. It assists the latter by producing dilatation of the skin vessels. The use is largely for the early stages of coryza.

Diabetes. Opium used to be administered to persons suffering from diabetes, and the amount of sugar in the urine often certainly diminishes as a result.

Contraindications. (1) Children under one year of age.

(2) Respiratory weakness, especially if associated with cyanosis and abundant bronchial secretion.

(3) Asthenic bronchitis, even though the physical signs be slight.

(4) Idiosyncrasy. Morphine may cause vomiting for three days after a single dose. In the absence of any history in relation to the drug, always start with a small dose, *e.g.* $\frac{1}{8}$ gr., and repeat after half an hour if all is well. In the event of symptoms of idiosyncrasy, heroin can often be substituted.

(5) Chronic painful diseases (but *see* "Pain").

(6) Certain states of cortical irritability, *e.g.* mania and meningitis, may be aggravated by morphine; this is not constant.

(7) Possibly severe renal disease. There is still great difference of opinion on the question of using morphine in uræmia. Small doses are often most efficacious in quelling uræmic convulsions, however.

(8) After operations on the biliary tract unless combined with glyceryl trinitrate, because of the rise of intrabiliary pressure which throws a further strain on the liver cells.

In advanced liver deficiency, only small quantities of opium or morphine should be given, if indicated, in view of the inability of this organ to carry out its part in the breakdown of the alkaloid, and in its storage.

Toxicology

Acute poisoning There may be slight preliminary excitability, but soon drowsiness sets in; this is followed by incapacity for exertion, sleep, and finally deep coma. The pupils are minutely contracted. At first the patient can be roused, but soon no stimulation will do this. Reflex action is abolished. The skin is cold, the face and lips are livid, and towards the end bathed in sweat. The pulse is weak and slow. The respiration becomes slower and more irregular, at last it is stertorous, and the patient dies from asphyxia.

Diagnosis of poisoning by opium. (1) *From alcoholic poisoning.* Often very difficult, especially if, as commonly happens, the man poisoned with opium has taken alcohol or had it given him. The pupils are contracted in opium poisoning. The patient is more easily roused in alcohol poisoning. Odour of poppy in breath if opium has been taken. (2) *From cerebral hœmorrhage.* If this is in the pons Varolii the pupils may be very contracted and the diagnosis difficult, but look carefully for paralyses and pyrexia. Usually cerebral hæmorrhage takes place into the internal capsule, and then the face and the limbs on the opposite side are paralysed. If the hæmorrhage is a small one, and especially if it is in the pons, the temperature may be raised; if it is a very large one the temperature falls for the first few hours, but may rise subsequently. If the pupils are unequal the case is one of cerebral hæmorrhage. (3) *From carbolic acid poisoning*, in which there may be coma and contracted pupils. The acid produces white patches in the mouth, and the odour is characteristic. (4) *From chloroform and ether poisoning* by the odour of the breath and of the vomited matters. (5) *From uræmia* by the signs of Bright's disease, especially albuminuria and hypertrophied heart. (6) *From diabetic coma* by the smell of the breath and the glycosuria. (7) *From the comatose stage of an epileptic fit* by the history, the dilatation of the pupils, and the fact that the lividity does not deepen. (8) *From the same stage of a fit in general paralysis* of the insane and other nervous diseases by the same symptoms.

Post mortem. The appearances after death from opium poisoning are those always found after fatal asphyxia.

Treatment. Wash out the stomach with dilute potassium permanganate solution (which decomposes morphine). Always rouse the patient by flapping him with a towel, pinching him, applying the faradic current, and putting ammonia to the nose ; $\frac{1}{40}$ gr. atropine sulphate given subcutaneously, and $\frac{1}{15}$ gr. strychnine ; nikethamide or preferably leptazol intravenously, and ephedrine hydrochloride intramuscularly are very valuable. 7 per cent. carbon dioxide in oxygen should be given by inhalation, and, if necessary, artificial respiration should be employed.

Chronic morphine poisoning. As many persons administer the drug subcutaneously to themselves, chronic poisoning is very common. The symptoms are that the patient loses all sense of right and wrong, he will lie and thieve in the most degrading way, especially if his desire is to obtain the drug, and absolutely no statement that he makes can be trusted. He neglects his work, and lets his business go to ruin. He wastes and becomes anæmic, he suffers from loss of appetite, indigestion, dry mouth, sluggish bowels, and a foul tongue. The nails are brittle, the skin dry, the hair turns grey early, and falls out. There is sexual impotence, no erections take place, no semen is secreted ; there is amenorrhœa, and the flow of milk is stopped, but there is polyuria. The pupils are small, and loss of muscular power, slight ataxy and tremor are present in severe cases. The arms or other parts are scarred with marks of the syringe, and 20 grains of morphine a day are sometimes taken.

The patient must be isolated and carefully watched to see that he gets no morphine (he often eludes or bribes his nurse) ; it should be diminished gradually, so that at the end of a fortnight he is taking none. If it is stopped suddenly there may be serious collapse and wild delirium. Relapses are very common, and a complete cure after a relapse is very rare.

Antagonism

Atropine. Atropine (alkaloid of belladonna) is an antidote to morphine, because it powerfully stimulates the respiratory centre. Caffein, strychnine and carbon dioxide have similar actions in this respect. It should not be overlooked that large doses of atropine ultimately paralyse the centres and, therefore, not more than $\frac{1}{40}$ gr. should be administered. It appears to be antagonistic to opium in other particulars, but is not really so. Thus, although it prevents perspiration and dilates the pupil, these effects are due to action on the peripheral nerve terminations, while morphine produces contrary results by acting on the central nervous system. Still it has been found that some of the undesirable effects that may follow the subcutaneous injection of morphine, such as vomiting and constipation, may be avoided if $\frac{1}{100}$ gr. of atropine sulphate is injected at the same time.

Papaveretum (B.P.C.). *Synonym.* Opium Concentratum. *Tr. Names.* Omnopon, Pantopon.

A solution of all the opium alkaloids as hydrochlorides freed from meconic acids, gums, resins, and dried.

Composition. Morphine, 52 per cent. ; narcotine, 20 per cent. ; codeine, 2 per cent. ; papaverine, 2·5 per cent. ; thebaine, 1 per cent. ; narceine, 1·2 per cent. ; other alkaloids, 4 per cent. ; water, 8 per cent. ; hydrochloric acid, 9 per cent.

It is grey powder. Readily soluble in water.

Dose, $\frac{1}{6}$—$\frac{1}{2}$ gr. **0·01—0·03 G.**—by mouth ; $\frac{1}{6}$—$\frac{1}{3}$ gr. **0·01—0·02 G.**—subcutaneously.

1 gr. papaveretum corresponds to 5 gr. opium.

Papaveretum is less toxic than morphine, and especially depresses the respiratory centre less ; it seldom causes vomiting, and is used extensively as an analgesic. The presence of papaverine prevents the sphincter spasm of morphine and therefore upsets digestion less.

Papaverinæ Hydrochloridum (B.P.). $C_{20}H_{21}O_4N,HCl$. A white crystalline water-soluble (1 : 40) alkaloid.

Dose, 2—4 gr. 0·12—0·25 G.

In therapeutic doses it has no effect on the nervous system. In large doses it increases reflex excitability owing to action on the spinal cord. It relaxes smooth muscle and it is used for this effect in therapeutics, especially in **arterial embolism.** Its effect here is to encourage dilatation of collateral vessels which may be contracted reflexly. It should be given intravenously. It is of little value in asthma or angina.

Narcotine acts like papaverine.

Narceine also resembles papaverine in action.

Dionine is ethyl morphine ; a white powder soluble in 8 parts of water. **Dose,** $\frac{1}{4}$ **gr.** Its action is like that of codeine.

Dilaudid. Dihydromorphinone hydrochloride. $C_{17}H_{19}O_3N,HCl$.

Source. A morphine derivative.

Characters. Colourless, bitter crystals.

Solubility : Free in water and alcohol.

Dose, $\frac{1}{16}$—$\frac{1}{8}$ gr. 0·004—0·008 G.
$\frac{1}{32}$—$\frac{1}{16}$ gr. 0·002—0·004 G.—by injection.

Action and Therapeutics

Dilaudid affects the respiratory centre in a manner similar to that of morphine. It also resembles morphine in the production of analgesia. It is about three times as powerful as morphine, but disturbs gut movement to a much slighter extent. In certain people it causes nausea.

It is used as a morphine substitute because its power of producing addiction is slight ; it does not cause severe constipation ; tolerance to it is developed more slowly and to a less extent than morphine. It falls under the **D.D.A.**

Pethidinæ Hydrochloridum (**B.P.**). $C_{15}H_{21}O_2N, HCl$. *Tr. Name.* Dolantin. A synthetic drug introduced as a substitute for morphine. It is ethyl-methyl-phenyl-piperidine carboxylic acid.

Dose, ⅖—1½ gr. 25—100 mg.

Preparation (B.P.)

Injectio Pethidinæ Hydrochloridi.

Dose, as above.

Action

Pethidine is an analgesic by virtue of its action on the brain. It appears also to reduce the sensitivity of the cough centre. It is claimed to have an antispasmodic effect on plain muscle by direct action and on the nerve endings and thus to combine the action of atropine, papaverine and morphine. It does not disturb digestion and it does not cause general depression of the higher cerebral centres. It may cause vomiting, nausea, and giddiness. Tolerance for Pethidine is not developed. It may produce euphoria and, therefore, addiction. It is less powerful than morphine.

Therapeutics

Pethidine has been used with success for the relief of **pain** and of **cough.** It is most effective when administered by injection. It is also a useful analgesic in **labour,** but does not produce amnesia unless combined with scopolamine. It has an antispasmodic action on the uterine cervix. The scheme recommended is 0·1 G. intramuscularly when the cervix is two fingers dilated, followed one hour later by the same dose and 0·5 mg. scopolamine.

It is also effective in the treatment of **status asthmaticus.**

Codeina (B.P.). Codeine. $C_{18}H_{21}O_3N,H_2O$.
SOURCE. An alkaloid obtained from opium or morphine.

Characters. Nearly colourless trimetric crystals. *Solubility:* 1 in 120 of cold water, 1 in 2 of alcohol (90 per cent.), 1 in 2 of chloroform.

Dose, ⅙—1 gr. 10—60 mg.

Codeinæ Phosphas (B.P.). Codeine Phosphate. $C_{18}H_{22}O_3N$, H_3PO_4, $2H_2O$.
Characters. White crystals, slightly bitter. *Solubility:* 1 in 3·5 of water.

Dose, ⅙—1 gr. 10—60 mg.

Preparations

1. Syrupus Codeinæ Phosphatis (B.P.C.). Codeine phosphate, 1; distilled water, 3; syrup, to produce 200. *Strength*: Ten millilitres contain 0·05 grm. of codeine phosphate; 1 fl. dr. contains 0·27 gr.

Dose, 30—120 min. 2—8 ml.

2. Tabellæ Codeinæ Phosphatis (B.P.). Contain ½ gr.—0·03 G. in each.

3. Tabellæ Codeinæ Compositæ. Similar to *Tr. Prep.* Veganin. Contain codeine phosphate, ⅛ gr.; aspirin, 4 gr.; phenacetin 4 gr.

Action and Therapeutics

Codeine is at least ten times weaker than morphine in its narcotic effect, but has one-quarter of its depressant action on the cough and respiratory centres. It is of little value in relieving pain. In large doses it excites the spinal centres. It is entirely excreted in the urine. It relieves cough, and for this the syrup of the phosphate is very useful. It was also used to diminish the glycosuria in diabetes; but it is doubtful whether it does this more effectually than opium. For diabetes it was given as a pill. The phosphate has the advantage of being much more soluble than codeine.

Dicodid. Dihydrocodeinone acid tartrate. Similar in action to dilaudid but less toxic.

Dose, ⅙—⅓ gr. 0·01—0·02 G.
⅛—¼ gr. 0·008—0·016 G.—by injection.

Thebaine produces powerful convulsions by its action on the cord. Its subsequent depressant action is very slight.

Diamorphinæ Hydrochloridum (B.P.). Diamorphine hydrochloride. $C_{21}H_{23}O_5N$, HCl, H_2O.
Unoff. Synonym. Heroin.

Source. An alkaloid obtained by the action of acetic anhydride on morphine.

Characters. A white, bitter, crystalline powder.

Dose, $\frac{1}{12}$—$\frac{1}{6}$ gr. 5—10 mg.

Action and Therapeutics

The drug resembles morphine in its general effects, but acts more strongly on the respiratory centre. It is, therefore, more dangerous than morphine. It is more depressant to the cerebral cortex than codeine, but less so than morphine. Its analgesic effect is about seven times stronger than that of morphine. It is excreted unchanged in the urine. Only a small degree of tolerance is acquired, and then most of the drug is destroyed in the body. No tolerance is developed towards its excitant action on the nervous system, so that convulsions may be produced in the place of sleep. Addiction is common.

This drug is used to allay cough, especially incessant cough, without much expectoration. It is also used to abolish pain as it is less liable than morphine to cause vomiting. Alarming symptoms of respiratory paralysis may, however, occur after therapeutic doses. Papaveretum is much safer and usually equally efficacious.

CANNABIS

Cannabis (B.P.C.). Cannabis Indica. Indian Hemp The dried flowering or fruiting tops of the pistillate plant of *Cannabis sativa*, from which the resin has not been removed.

Composition. The active constituent is a resin whose active principle is cannabinol.

Preparations (B.P.C.)

1. **Extractum Cannabis.** Alcoholic.

Dose, ¼—1 gr. 0·016—0·06 G.

2. **Tinctura Cannabis.** Extract, 1 ; alcohol (90 per cent.), 20. Simple solution.

Dose, 5—15 min. 0·3—1 ml.—should be triturated with mucilage before water is added, as this precipitates the very bulky resin.

Tincture of Indian Hemp is contained in Tinctura Chloroformi et Morphinæ Composita.

Haschisch is a confection of the drug. Gunjah, or ganga, is the dried flowering tops of the cultivated female plants which are coated with resin. Churrus, or charas, is the resin scraped off the leaves. Bhang is the dried leaves ; in some provinces it means powdered ganga made into a drink. Ganga and charas are often smoked like tobacco. Marihuana is the name applied to the leaves as grown and smoked in the U.S.A. and South America.

Action

External. None is known.

Internal. The absorption of cannabis is greatly facilitated if the drug be taken one hour before a meal. Its action is then felt within two hours of administration. If taken after a meal, no result may be apparent for as long as six hours. The effects of cannabis vary very much in different people. This is partly due to the uncertain strength of the preparations of the drug and partly to individual peculiarities, but generally the symptoms are somewhat as follow. After some time, usually from half an hour to two or three hours, there is a pleasurable sensation of mild intoxication ; the patient is particularly gay, joyous and pleased with everything ; he will laugh and smile on the slightest provocation, and is himself able to say sharp, witty things. Pleasant ideas and visual hallucinations flit through his mind with wonderful rapidity, so that time seems to him much extended. Generally the ideas are quickly forgotten, but sometimes the memory of them remains after recovery. The eyes are bright, the conjunctivæ injected, the pupils may be dilated. The limbs feel heavy, and there is a marked lowering of general sensibility, so that he scarcely feels a severe pinch ; this may pass on to complete anæsthesia. After a time sleep, which is often accompanied by delightful dreams, comes on. On awaking, the subject is refreshed but everything about him feels unreal for an hour or so. There is no constipation or headache. If sleep is resisted, the effect of the drug wears off in two to three hours, leaving in its wake a pleasant drowsiness and not infrequently a voracious appetite. It is taken in the East to produce the early pleasurable symptoms, and, in moderation, it causes no harm. Very few take it to excess, but in them it leads to loss of appetite and strength, trembling, epilepsy, and insanity. Cannabis may act as an aphrodisiac by virtue of the lack of inhibition and the erotic images which it produces. The most constant effect is that time and space seem indefinitely prolonged. Minutes appear to be days. Large doses given to a dog only made him sleepy, and uncertain on his legs, but he appeared contented and pleased. Much the same results followed when a monkey was made to inhale the smoke daily for 181 days.

The action is a combination of stimulation and depression of the cerebral cortex. The latter effect predominates when the drug is taken by mouth, and when the subject is undisturbed. Enormous doses have been recovered from.

Therapeutics

The drug has been used medicinally for 2,000 years. It has been given with success in migraine and neuralgia, but it very often fails to afford relief. It is used for depressive mental conditions and anxiety states notably when associated with duodenal ulcer. It is useful for insomnia associated with pain because it combines analgesic with soporific action. The tincture is very difficult to prescribe, because of the voluminous precipitate of resin which falls on the addition of water. Mucilage must be used to suspend it, and the taste should be covered with spirit of chloroform.

APOMORPHINE

Apomorphinæ Hydrochloridum (B.P.). Apomorphine Hydrochloride. $(C_{17}H_{17}O_2N, HCl)_2, H_2O$.

Source. It is the hydrochloride of an alkaloid obtained from morphine. The morphine loses one molecule of water.

Characters. Small greyish-white, shining needles, turning green on exposure to light and air; faintly acid. *Solubility:* 1 in 50 of water, 1 in 50 of alcohol (90 per cent.).

Emetic

By subcutaneous injection

Dose, $\frac{1}{32}$—$\frac{1}{8}$ gr. 2—8 mg.

Preparation **(B.P.)**

Injectio Apomorphinæ Hydrochloridi. Contains 3 mg. ($\frac{1}{20}$ gr.) in 1 ml. (15 min.).

Dose, $\frac{1}{32}$—$\frac{1}{8}$ gr. 2—8 mg.

Action

External. None.

Internal. *Gastro-intestinal tract.* Apomorphine is the most powerful **emetic** we possess. It does not act locally on the stomach, but solely on the vomiting centre in the medulla. It is therefore an indirect emetic. This is shown by the fact that when the drug is injected subcutaneously it produces violent vomiting if the vessels are so tied that none can reach the stomach, but not if they are so tied that it cannot reach the medulla.

Circulation. Therapeutic doses have no effect beyond the depressing action which may be attributed to the vomiting.

Respiration. This is at first stimulated by the act of vomiting. The effect of poisonous doses is doubtful; probably they depress respiration. If the bronchial secretion is thick and viscid it is rendered more fluid by apomorphine.

Nervous system. The result of toxic doses is to cause great restlessness and excitability in animals, followed by depression. In man the stimulant action on the vomiting centres resembles in exaggerated form that often seen by the parent substance, morphine. No deaths from its use have been recorded.

Therapeutics

Vomiting action. The advantages of apomorphine over other emetics are that it is certain, prompt, and powerful; it can be given when emetics introduced directly into the stomach would not act, and it does not irritate the stomach. It is largely used in cases of poisoning. It is usually given hypodermically. As solutions will not keep, it is advisable to use gelatin discs of apomorphine hydrochloride, which can be dissolved as required.

Expectorant action. It is rarely used for this except in cases of bronchitis in infants associated with excessive secretion and cyanosis. The act of vomiting often results in expulsion of the muco-pus, and the child may then make favourable progress.

BELLADONNA

Belladonnæ Herba (B.P.). *Synonyms.* Belladonnæ Folium. Belladonna Leaf. The leaves of *Atropa Belladonna* (Deadly nightshade).

Strength: Belladonna leaves must yield not less than 0·3 per cent. of alkaloids, calculated as hyoscyamine.

COMPOSITION. The chief constituents are—(1) *Atropine*, which is racemic hyoscyamine. (2) *Hyoscyamine*. Atropine is optically inactive because it consists of equal parts of lævorotatory and dextrorotatory hyoscyamine.

Preparations (B.P.)

1. **Belladonna Præparata.** Powdered belladonna leaf. *Synonym.* Pulvis Belladonnæ.

SOURCE. Belladonna leaf reduced to a fine powder and adjusted, if necessary, by the addition of powdered, exhausted belladonna leaf to contain 0·3 per cent. of alkaloids, calculated as hyoscyamine.

Dose, ½—3 gr. 30—200 mg.

2. Extractum Belladonnæ Siccum. Prepared from the leaves by percolation with alcohol (70 per cent.). *Standardized to contain* 1 *per cent. of the alkaloids.*

Dose, $\frac{1}{4}$—1 gr. 15—60 mg.

3. Tinctura Belladonnæ. Belladonna leaves, dried and powdered, 1; alcohol (70 per cent.), q.s. *Standardized to contain* 0·03 *per cent. of total alkaloids.*

Dose, 5—15 min. 0·3—1 ml.

Belladonnæ Radix (B.P.). Belladonna Root. The root of *Atropa Belladonna*, collected in the autumn and dried.

Composition. As of the leaves. Contains 0·4 per cent. of alkaloids, calculated as hyoscyamine.

Preparations **(B.P.).**

1. Extractum Belladonnæ Liquidum. Prepared by percolation of the root with alcohol (90 per cent.) and water. *Standardized to contain* 0·75 *per cent. of the alkaloids of the root.*

2. Linimentum Belladonnæ. Belladonna root, camphor, alcohol (80 per cent.). *Strength:* 0·375 per cent. of alkaloids.

3. Suppositorium Belladonnæ. Liquid extract, 0·15 ml. *Strength:* Each contains 0·001 G. (about $\frac{1}{60}$ gr.) of the alkaloids.

Atropina (B.P.). Atropine. $C_{17}H_{23}O_3N$.

Source. An alkaloid obtained from Atropa belladonna and other plants of the order Solanaceæ.

Characters. Colourless acicular crystals. *Solubility:* 1 in 500 of cold water, 1 in 1 of chloroform, 1 in 1 of alcohol (90 per cent.), 1 in 16 of ether.

Composition. Atropine is optically inactive hyoscyamine, containing lævohyoscyamine and dextro-hyoscyamine in equal proportions.

Atropinæ Sulphas (B.P.). Atropine Sulphate. $(C_{17}H_{23}O_3N)_2$, H_2SO_4, H_2O.

Source. It may be obtained by neutralizing atropine with diluted sulphuric acid.

Characters. Nearly colourless, crystalline substance. *Solubility:* 2 in 1 of water, solution neutral; 1 in 4 of alcohol (90 per cent.).

Dose, $\frac{1}{240}$—$\frac{1}{60}$ gr. 0·25—1 mg.

Preparations **(B.P.)**

1. Lamella Atropinæ. Discs containing in each atropine sulphate, $\frac{1}{5000}$ gr. (0·013 mg.).

2. Oculentum Atropinæ. An ointment for the eye containing 0·25 per cent. of atropine sulphate.

3. Oculentum Atropinæ cum Hydrargyri Oxido. An ointment for the eye containing atropine sulphate 0·125 per cent.; yellow mercuric oxide, 1 per cent.

4. Tabellæ Atropinæ Sulphatis. Contain $\frac{1}{100}$ gr.—0·6 mg. in each.

5. Injectio Atropinæ Sulphatis. Contains 0·6 mg. ($\frac{1}{100}$ gr.) in 1 ml. (15 min.).

Dose, $\frac{1}{240}$—$\frac{1}{60}$ gr. 0·25—1 mg.

Action

The actions of belladonna and atropine are the same.

External. Atropine placed by itself upon the unbroken skin cannot be absorbed, but rubbed in with substances which are absorbed, such as alcohol, glycerin, or camphor, or applied to a broken surface, it paralyses the terminations of the sensory nerves. It is thus a **local anæsthetic.** To a much less extent it locally paralyses the terminations of the motor nerves, first contracts and then dilates the vessels, and renders the secretions of the skin less active.

Internal. Atropine prevents the access of acetylcholine to the effector organs. Its peripheral nervous action is, therefore, largely that of paralysis of the cranio-sacral division of the autonomic nervous system.

Secretory nerves. The **adeno-neural junctions of all the secretory nerves** in the body are **depressed**, so that the secretions of those glands, whose activity is essentially regulated by their nerve supply, are markedly diminished. Thus even small doses of atropine make the **mouth dry** from lack of saliva and mucus. In health, secretion of submaxillary saliva always follows stimulation of the chorda tympani nerve, and, as is well known, this is due to the fact that this nerve is the secretory nerve for this gland, and not to any vascular dilatation. If atropine be given to an animal, stimulation of the chorda no longer causes an increased flow of saliva, however close to the gland the nerve is excited, the reason being that atropine has paralysed the terminal junctions of the chorda tympani. In the same way the terminations of the secretory nerves of the other salivary glands and the mucous glands are paralysed, and hence the mouth is dry, because normal impulses cannot reach the cells of the glands.

Stomach, pancreas, and intestines. Atropine diminishes the secretions of these by paralysing the nerve endings of the vagus. In man it has no constant effect on gastric acidity but tends to depress it. It is a powerful anti-spasmodic and relaxes gastric and pyloric spasm. The secretion of bile is unaffected.

Sweat glands. Atropine paralyses the terminations of the nerves in the sudoriparous glands. Thus the **skin** becomes **dry.** Likewise tears are lessened.

Kidneys. Atropine has no direct effect on the secretion of urine.

Bronchial mucous membrane. The secretion of **bronchial** and **tracheal mucus**, like that of the mouth, is **diminished.**

Mammary gland. Belladonna has no effect on mammary secretion, for this is largely independent of nerve supply.

Sensory nerves. It has already been mentioned that belladonna rubbed into the skin depresses the function of the terminations of the sensory nerves. This action is not exerted when given by mouth. Even the local effect is feeble.

Voluntary muscles and their nerves. Voluntary muscles are quite unaffected even by toxic doses of atropine ; towards the end of a case of belladonna poisoning the motor nerves are slightly paralysed.

Involuntary muscles. In therapeutic doses, atropine reduces peristaltic activity, though the nervous control is unaffected. Its most striking effect is seen on the violent contractions induced by irritation from purgatives. These are completely inhibited by small doses. The same effect is seen on the colics of renal and gall-bladder disease. In large doses, Auerbach's plexus is stimulated and purgation results.

The same effect is seen on other organs containing unstriped muscle, *e.g.* bile ducts, bladder, ureters, urethra, vesiculæ seminales, uterus, and spleen.

In all these cases the action is seen almost exclusively in its sedative effect on **abnormal contractions** produced by various drugs. It does not interfere with the normal contraction or relaxation resulting from stimulation of the nerve supply.

The eye and its nerves. Atropine acts only on the terminations of the nerves in the involuntary muscles of the eye. If it be dropped into the eye or given by the mouth, the **pupil dilates widely,** and cannot be made to contract by stimulation of the third nerve. That this dilatation is not due to any marked action on the muscular fibres of the iris themselves is shown by the fact that the atropinized pupil will contract if the muscle itself be stimulated. Therefore it must be that the **terminations of the third nerve** in the iris **are paralysed.** The termination of the oculo-motor nerve must be recognized as the myoneural junction (*vide supra*), for atropine still antagonizes pilocarpine even after complete degeneration of the third nerve. The ending of this nerve in the ciliary muscle is affected in the same way, and consequently **accommodation is paralysed.** It is certain that this mydriasis and defective accommodation is in no part central, as is the contraction of the pupil produced by opium. So strong is the local action of belladonna, that if atropine be dropped into the recently excised eye the pupil will dilate. When the third nerve is cut the pupil dilates, and if after this atropine be dropped into the eye it dilates still further. Thus atropine also stimulates the terminations of the sympathetic in the iris; but this action is comparatively slight; the chief result is increased tonus of the radiating fibres causing dilatation because the nerve endings of the circular are paralysed by atropine. The intra-ocular tension is increased by large doses, particularly when it is already high as in glaucoma. There is, as a result of the paralysis of the ciliary muscle, disturbance of vision. Atropine does not act on the pupils of birds.

The heart and its nerves. The main action of atropine is **to paralyse the myoneural junctions of the vagus** in the heart, and consequently the **pulse is rendered more rapid,** and cannot be slowed by strongly stimulating the vagus. If the rate of the heart has been lowered by muscarine, which can be shown to have a local stimulating influence on the terminations of the vagus in the heart, the application of atropine renders the heart quick again, the two drugs being, in their effect on the heart, exactly antagonistic. This quickening of the pulse from inhibition of the vagal cardiac terminal filaments is the chief action of atropine on the heart. The increase of rate depends upon the degree of inhibition normally exerted by the vagus. This is very slight in children and the aged, in whom atropine may cause no appreciable acceleration of pulse. The transient slowing of the pulse following administration of atropine is due either to direct action on the heart muscle, or stimulation of the vagal centre. Although the **pulse** is quickened by belladonna, its **force is not diminished.** Toxic doses depress the function of the cardiac muscle by direct action.

Vaso-motor system and its nerves. After a considerable dose of belladonna the **skin is flushed,** and a scarlatiniform erythematous rash may be present in belladonna poisoning. It is thus obvious that such a dose of belladonna relaxes the peripheral vessels. The exact cause of this has not definitely been made out, but it is extremely probable that it is not a peripheral action but is due to stimulation of the vaso-dilator centre, for it disappears on section of the cervical sympathetic. Certain individuals possessed of an idiosyncrasy towards this drug exhibit a rash even after small doses (*e.g.* $\frac{1}{200}$ gr.). Owing to the action on the terminations of the vagus in the heart causing increased rapidity of beat, the **blood pressure rises** somewhat; **subsequently it falls** when the heart itself is paralysed.

Respiration and its nerves. Here also belladonna **paralyses peripheral nerve endings,** in this case those of the vagus in the bronchial tubes. The result is that the **muscular coat** of the bronchial tubes is **relaxed,** and that the secretions are diminished. The respiratory centre is first stimulated, and so the respirations are quicker and deeper. Large doses may produce convulsions which interfere with breathing, which may be thus permanently arrested. Otherwise the centre is eventually paralysed and this is the cause of death.

Temperature. This is decidedly **raised** by toxic doses of belladonna (it may be four degrees Fahrenheit or more). This rise is independent of the circulatory changes and convulsions. It is said that heat-production is greatly exaggerated. The heat-loss is also increased, probably because the flushing of the skin leads to a greater loss by radiation.

Central nervous system. A considerable dose of belladonna causes **delirium,** showing that the higher centres are stimulated, particularly those concerned with motor activity. The effect spreads downwards to the medulla and even the spinal cord, and thus causes convulsions. Stimulation is followed by paralysis. Other symptoms that may be observed with large doses, and which are probably due to disorder of the brain, are visions, staggering gait, and giddiness.

Absorption and excretion. Atropine is rapidly absorbed and may be found in all the organs of the body. About half the atropine ingested appears in the urine chiefly unchanged, partly as tropine. A little passes into the milk and through the placenta. The remainder is oxidized in the liver.

It will be seen that the **dominant action** of belladonna is to **depress** the nerve endings of cardiac and unstriped muscle and glands ; this effect is not confined to one or other division of the autonomic system, but has a predilection for the para-sympathetic. Its action is explained by its preventing acetyl-choline, liberated at nerve-endings, acting on the effector structure. In addition, it **first stimulates** and **then depresses** the central nervous system.

The peripheral action is due to the lævo-rotary hyoscyamine moiety : the dextro-rotary fraction has only a central effect.

Children may take relatively large doses of belladonna without any symptoms of poisoning.

Pigeons and rodents are peculiarly insusceptible to it.

Therapeutics

External. *Skin.* Belladonna plasters were at one time in frequent use in the treatment of such painful conditions as lumbago, phlebitis and arthritis. It is probable that any benefit they conferred was due to support, for the analgesic action is extremely slight, even though the drug be presented in a suitable vehicle to aid penetration. Sufficient may be absorbed, however, to produce poisoning. A similar use to arrest the secretion of milk is unjustifiable on pharmacological grounds; good results were due to firm bandaging.

Eye. A few drops of a 1 in 2,000 solution may be used to dilate the pupil for purposes of ophthalmoscopic examination. To paralyse accommodation for the same reason, or in the treatment of certain inflammatory states, a 1 per cent. solution may be used as 1 drop twice a day for three days, or the oculenta may be employed. The paralysis lasts for a week, and the pupil may be dilated for several days longer. Poisoning may occur from prolonged use in the eye. *Atropine must never be used in the eye if there is any tendency to glaucoma.* The result will be disastrous, for neither pilocarpine nor eserine will effectively counteract its prolonged action. In elderly people, therefore, homatropine should be used.

Atropine Methylnitrate (Eumydrine) is a useful mydriatic, the effect appearing in half an hour and passing off in twelve hours. Its toxicity in man is probably about seven times less than that of atropine. A 1–2 per cent. solution is used. It has largely replaced surgery in the treatment of congenital pyloric stenosis of infants. It is given in doses of 0·25 to 0·5 mg. in solution (this is unstable) six times daily half an hour before feeds until for a week there has been no vomiting. Dehydration and alkalosis, when present, must be rectified by the introduction of saline and glucose by a suitable route before treatment is commenced, otherwise the child will be poisoned. Six mgm. four-hourly may be given by mouth to reduce gastric and duodenal spasm in case of **peptic ulceration**

Internal. *Central nervous system.* Atropine has been employed to check salivation in **parkinsonism.** The muscular rigidity of this disease is often strikingly relieved by full doses of belladonna, stramonium, or scopolamine. A combination of atropine sulphate, hyoscyamine, and hyoscine hydrobromide in doses of 0·037, 0·45, and 0·011 mg. respectively is claimed to be especially effective as the result of synergism. It is an excellent prophylactic for **sea-sickness.**

Alimentary tract. The tincture of belladonna is often given in cases of gastric and **duodenal ulcer.** Its beneficial action is due to its allaying excessive peristalsis and spasm. Hyoscyamine sulphate, gr. $\frac{1}{100}$ twice daily is very effective in this respect. Intestinal colic from various causes is relieved by belladonna or its alkaloids. The extract is commonly combined with some purgative in a pill to relieve colic.

Skin. Atropine will sometimes arrest sweating, and may succeed with the night sweats of phthisis.

Circulation. Atropine is seldom used for its effect on the heart. As a diagnostic aid it may be employed to determine whether bradycardia is due to disease of the heart muscle rather than to vagal inhibition. Thus **Marris's test** for typhoid consists of the injection of $\frac{1}{33}$ gr. atropine. An increase of less than 10 beats per minute is suggestive of typhoid or paratyphoid. This dose in healthy persons between sixteen and forty years of age usually results in a rise of pulse rate by 20 to 50 beats.

A similar dose has been recommended to be given prior to paracentesis thoracis, to avoid the danger of death from vagal inhibition of the heart.

Respiration. As belladonna relaxes the muscular coat of the bronchial tubes it is of some value in spasmodic affections of the respiratory passages. Thus it has been given for whooping-cough. It is also useful in **asthma,** and in bronchitis with asthma-like paroxysms ; its powerful stimulation of the respiratory centre and its capability of diminishing the secretion will, in properly chosen cases, render it particularly valuable. It is helpful in pulmonary œdema and in broncho-pneumonia. It is used as a pre-anæsthetic, particularly before the administration of ether. Its value lies in the reduction of bronchial secretion.

Genito-urinary diseases. Belladonna is used for the nocturnal incontinence of children, and it occasionally overcomes this trouble in adults when it is not due to organic disease. Ephedrine is more efficient in this respect. Its power of relieving the spasm of involuntary muscle is well shown in the effectual manner in which the very painful vesical spasm which accompanies calculus, cystitis, and prostatitis may be benefited by it.

Toxicology

If a person takes a moderate dose of belladonna he soon experiences dryness of the mouth and throat, and as the food, therefore, cannot be properly lubricated, there is difficulty of swallowing ; the pulse may at first be a little slower than usual. The pupil is dilated ; accommodation is defective, and vision confused. The skin feels dry. If the dose has been a large one, these symptoms all come on quickly ; the conjunctivæ and face, and perhaps other parts of the skin, are flushed, and the rate of the pulse is greatly increased, it may even be doubled. The patient staggers, feels giddy, and reels when he walks ; the throat soon becomes very hot, the skin still more flushed, the eyelids swell, and there may be a uniform erythematous rash. The temperature is often raised, the respirations are slow and deep. The pupils are very widely dilated. By this time the patient is quite delirious. There may be purging, but this is not common ; and sometimes he complains of a frequent desire to micturate, although he is unable to pass any urine. Death takes place from respiratory failure. *Post mortem.* The organs are all in a state of venous congestion, which is due to the asphyxia. If recovery takes place the patient may have no recollection of his illness.

Treatment. Give emetics or wash out the stomach. Pilocarpine is useless because it does not antagonize atropine in the brain. This is the danger point. Chloroform for the convulsive stages. Morphine is valuable, but must be given in moderate doses because it supplements the subsequent depression of the respiratory centre produced by atropine. In the stage of depression, employ artificial respiration and CO_2 and O_2 inhalation.

Antagonism

The antagonism between atropine and morphine has already been discussed. It is clear that as *pilocarpine* stimulates the terminations of the secretory nerves in the salivary and sweat glands, and also excites the terminations of the third nerve in the iris and ciliary muscle, it is a diaphoretic, a sialogogue, and a myotic, and is in these respects antagonistic to atropine. *Physostigmine* also causes contraction of the pupil and spasm of the ciliary muscle by stimulation of the terminations of the third nerve, and it depresses the respiratory centre almost from the beginning. In these points it is an antagonist to atropine.

Homatropinæ Hydrobromidum (B.P.). Homatropine Hydrobromide. $C_{16}H_{21}O_3N,HBr$.

Source. It is the hydrobromide of homatropine prepared from tropine and mandelic acid.

Characters. A white crystalline powder or aggregation of minute trimetric crystals. *Solubility:* 1 in 6 of water, 1 in 18 of alcohol (90 per cent.).

Preparation (B.P.)

Lamellæ Homatropinæ. Discs containing $\frac{1}{100}$ gr. (0·6 mg.) of homatropine hydrobromide.

Action and Therapeutics

Homatropine has an action similar to that of atropine. It is only used to dilate the pupil in ophthalmic practice, the advantage over atropine being that the dilatation produced by homatropine passes off in a quarter of the time. It may be applied either as a solution (4 gr. of the hydrobromide to 1 fl. oz. of distilled water) or as the lamella. Furthermore its effect can be antagonized more readily by physostigmine—an important consideration when dealing with glaucoma.

STRAMONIUM LEAVES

Stramonium (B.P.). The dried leaves of *Datura stramonium.*

Composition. Chiefly hyoscyamine with a little atropine and hyoscine. It should contain not less than 0·25 per cent. of the alkaloids, calculated as hyoscyamine.

Preparations (B.P.)

1. Extractum Stramonii Liquidum. Contains 0·25 per cent. w/v of the alkaloids of stramonium, calculated as hyoscyamine.

Dose, ½—3 min. 0·03—0·2 ml.

2. Extractum Stramonii Siccum. Contains 1 per cent. of the alkaloids of stramonium, calculated as hyoscyamine.

Dose, ¼—1 gr. 15—60 mg. In post-encephalitic and similar conditions,

1—8 gr. 60—500 mg.

3. Tinctura Stramonii. Contains 10 per cent. of liquid extract of stramonium in 45 per cent. alcohol.

Dose, 5—30 min. 0·3—2 ml.

Action

The action of stramonium is that of the contained alkaloids (*q.v.*).

Therapeutics

Stramonium may be employed for the same purposes as belladonna, but it is rarely used, except in **paralysis agitans,** especially that form which follows encephalitis lethargica, and in cases of **asthma** to relieve the spasm of the bronchial tubes. The leaves are prescribed for the former condition because absorption of the alkaloids from the alimentary tract is more gradual, and the effect is thus spread out more, than if the extract or tincture were used. For asthma, powders of the leaf with lobelia and nitre are burned in a small heap or smoked as cigarettes: the vapour is inhaled. Himrod's, Bliss's, and other "cures" for asthma are of a similar composition. The objection to the use of these powders is that the fumes irritate the bronchi and are liable to set up bronchitis.

HENBANE

Hyoscyamus (B.P.). *Synonym.* Hyoscyamus Leaves. The leaves of *Hyoscyamus niger*. Collected from flowering plants and dried.

Composition. The chief constituents are—(1) *Hyoscyamine*, an alkaloid, also contained in belladonna, stramonium, and many other plants of the Natural Order *Solanaceæ*. It, like atropine, with which it is isomeric, consists of tropic acid and tropine. Lævohyoscyamine and dextrohyoscyamine both exist. Hyoscyamine is very unstable and becomes converted into atropine on keeping. (2) *Hyoscine*. (3) *Atropine*. Hyoscyamus should contain not less than 0·05 per cent. of the alkaloids; calculated as hyoscyamine.

Preparations (B.P.)

1. Extractum Hyoscyami Siccum. An alcoholic (70 per cent.) extract.

Standardized to contain 0·3 *per cent. of the alkaloids of hyoscyamus.*

Dose, ¼—1 gr. 16—60 mg.

2. Extractum Hyoscyami Liquidum. Hyoscyamus and alcohol (70 per cent.). Contains 0·05 per cent. of the alkaloids.

Dose, 3—6 min. 0·2—0·4 ml.

3. Pilula Colocynthidis et Hyoscyami. Dry extract of hyoscyamus, 12·5; aloes, 25; scammony resin, 25; oil of clove; curd soap; syrup of glucose.

Dose, 4—8 gr. 0·25—0·5 G.

4. Tinctura Hyoscyami. Liquid extract of hyoscyamus, 1; alcohol, 10.

Dose, 30—60 min. 2—4 ml.

Hyoscinæ Hydrobromidum (B.P.). Hyoscine hydrobromide $C_{17}H_{21}O_4N, HBr, 3H_2O$. *Synonym.* Scopolamine hydrobromide. The hydrobromide of an alkaloid, hyoscine or scopolamine, obtained from various plants of the natural order Solanaceæ. Decomposes to tropine and oscine.

CHARACTERS. Colourless, small, transparent, rhombic crystals, slightly bitter taste. *Solubility:* Freely in water and alcohol (90 per cent.).

Dose, $\frac{1}{200}$—$\frac{1}{100}$ gr. 0·3—0·6 mg.

Preparations (B.P.)

1. Oculentum Hyoscinæ. Contains 0·125 per cent. of hyoscine hydrobromide.

2. Injectio Hyoscinæ Hydrobromidi. Contains 0·4 mg. ($\frac{1}{160}$ gr.) in 1 ml. (15 min.).
Dose, $\frac{1}{200}$—$\frac{1}{100}$ gr. 0·3—0·6 mg.

Hyoscyaminæ Sulphas (B.P.C.). Hyoscyamine Sulphate. $(C_{17}H_{23}O_3N)_2, H_2SO_4$. The sulphate of an alkaloid, hyoscyamine, obtained from various plants belonging to the natural order Solanaceæ.

CHARACTERS. A crystalline, deliquescent, odourless, bitter powder. *Solubility:* 2 in 1 water; 1 in 4½ alcohol (90 per cent.).

Dose, $\frac{1}{100}$—$\frac{1}{200}$ gr. 0·3—0·6 mg.

Action

Hyoscyamine has the same effect as atropine, but **acts twice as strongly on the peripheral points** of action. This is due to its consisting entirely of the active lævo-rotatory isomer, whereas atropine contains equal parts of this and the dextro-rotatory form. On the other hand, **atropine and hyoscyamine have the same power**

to stimulate and then depress the central nervous system.

Hyoscine, or **Scopolamine,** closely resembles hyoscyamine in its peripheral action, affecting nerve endings twice as strongly as atropine. As a rule **the brain is depressed** by quite small doses (*e.g.* $\frac{1}{150}$ gr.) and drowsiness or sleep produced. Occasionally it excites the motor areas like atropine instead of inducing sleep, and large doses do not deepen the sleep, but give rise to delirium. The respiratory centre is always depressed.

Therapeutics

Hyoscyamus might be used for the same purposes as belladonna, but is chiefly employed in combination with purgatives to diminish griping. It is also given to relieve vesical spasm in calculus, cystitis, and prostatitis.

Hyoscine is employed as a cerebral depressant, and is used in **acute mania,** delirium tremens, febrile delirium, and insomnia, sometimes with good results. The impure forms contain both lævo- and dextrorotatory hyoscine, but both are active on the brain ; only the former has an appreciable peripheral effect. It is often given in asylum practice, but must be used carefully, as the activity of different specimens varies, and fatal results have followed its use. It should never be employed if the patient is weak. Hyoscine is usually given subcutaneously. A single dose should rarely exceed $\frac{1}{100}$ gr. (0·6 milligrm.) of the hydrobromide. Hyoscine is used extensively in the treatment of **paralysis agitans,** in which it may produce the same, or greater, beneficial effects as those seen under belladonna. Slight tolerance is developed, and the dose is thus raised gradually to $\frac{1}{50}$ gr. thrice daily. Prescribed with caffeine and pilocarpine to counteract the drowsiness and the dryness of the mouth, it may be taken for years with occasional intermissions. Eserine should be applied to each eye daily ; the patient is thus enabled to read. The action is thought to be one of depression of the extra-pyramidal tracts, but the similar effect of belladonna is difficult to explain. Combined with morphine it is given to diminish sensibility before a general anæsthetic and in labour (twilight sleep). It is used to prevent **sea-sickness.**

Hyoscyamine may be used for the same purposes as belladonna or hyoscine, but it is less effective as a cerebral depressant compared with hyoscine. It is used to relieve the pain of various abdominal colics and as a **mydriatic.** It is of great value in allaying the excessive peristalsis exhibited by the stomach in most cases of **duodenal ulcer.** It also reduces the hyperacidity of this disease. It prolongs the emptying rate of the stomach.

CAFFEINE

Caffeina (B.P.). Caffeine. $C_8H_{10}O_2N_4, H_2O$.

SOURCE. An alkaloid usually obtained from the dried leaves of *Camellia sinensis*, common tea, or from certain other plants, or prepared synthetically.

CHARACTERS. Colourless, silky, inodorous, acicular crystals. *Solubility:* 1 in 80 of cold water, 1 in 1 of boiling water, 1 in 40 of alcohol (90 per cent.). The solubility of caffeine is increased if sodium salicylate or sodium benzoate is added. Tea contains 3 to 5 per cent. (hence the name theine) and theophylline. Coffee, 1·3 per cent. (coffee leaves contain much more). Maté (Paraguay tea, the leaves of *Ilex paraguayensis*), 0·5 per cent. Kola nut (which is used as a beverage in Africa), 3 per cent.; this is the fruit of *Sterculia acuminata*. Most of these substances, and particularly cocoa, also contain theobromine. Caffeine is trimethyl-xanthine, theobromine and theophylline are dimethyl-xanthine, and are isomers. They are feeble alkaloids, their salts being very liable to split up.

Dose, 5—10 gr. 0·3—0·6 G.

Caffeina et Sodii Benzoas (B.P.). Caffeine and Sodium Benzoate.

SOURCE. Mix equal parts of caffeine and sodium benzoate, moisten with water and dry.

CHARACTERS. White powder completely soluble in 4 parts of water.

Dose, 5—15 gr. 0·3—1 G.
2—5 gr. 0·12—0·3 G.—by injection.

Preparation (B.P.)

Injectio Caffeinæ et Sodii Benzoatis. Contains 0·25 G. ($3\frac{3}{4}$ gr.) in 1 ml. (15 min.).

Dose, 2—5 gr. 0·12—0·3 G.

Action

External. None.

Internal. *Alimentary canal.* Excessive tea-drinking may cause indigestion, but this is probably induced by the tannin in the tea, and not by the caffeine. Coffee is, with some persons, slightly laxative; it is not known to what ingredient this is due.

Circulation. The xanthines, especially theophylline, stimulate the myocardium directly, causing increase of rate, amplitude of excursion, and cardiac output. The direct action also accounts for extrasystoles common in excessive tea-drinkers. The cardiac accelerator effect may be counterbalanced by stimulation of the vagal nuclei in the medulla. It is, therefore, impossible to foretell the effect of xanthines on the heart-rate.

Vessels. Intravenous injection of the xanthines dilates the coronary arteries. Caffeine has very little or no effect on the blood pressure, because although it stimulates the vaso-constrictor centre, it dilates arterioles by direct action on their walls.

Respiration. In animals the rate and extent of breathing are increased by caffeine from stimulation of the respiratory centre.

Nervous system. It is well known that tea and coffee **stimulate** the **cerebrum.** This is due to the caffeine in them. The patient becomes wakeful, the mental activity and capability for work are increased, the reasoning powers being quite as much affected as the imagination. In this respect the cerebral stimulation of caffeine differs from that of atropine in that whereas the former stimulates chiefly the psychical process, the latter stimulates the motor functions. Strychnine exerts its main effect at yet lower levels, chiefly in the cord. The special senses are rendered more alert. Very excessive tea-drinking causes trembling of all the muscles of the body, and makes the patient extremely " nervous."

Caffeine in larger doses stimulates the **medullary centres,** but the effect is seldom noticeable in man, unless there has been previous depression of the respiratory centre, *e.g.* by morphine. Cheyne-Stokes respiration may be abolished by the xanthines.

In man the spinal cord and muscles are very little affected by caffeine, but in some frogs the spinal cord is decidedly stimulated, and convulsions occur. In man the power to do muscular work is increased by caffeine. This in ordinary doses is due to central action and not to the power of increasing irritability and contractility of muscle by direct action, as seen in animal experiments. Motor and sensory nerves are uninfluenced in all animals. Theophylline acts like caffeine. Theobromine acts like both these drugs peripherally, but does not stimulate the brain or cord.

Smooth Muscle. The xanthines cause relaxation of smooth muscle especially if previously constricted. This is best shown in asthma. Theophylline is the most powerful in this effect.

Kidneys. Caffeine causes a great increase in the amount of urine—chiefly its fluids, but to a less extent its solids—by reducing resorption in the tubules. It also acts by causing a transfer of chloride from tissues to plasma which again results in diuresis. Caffeine does not injure the kidney. The drug is a good **diuretic,** but theobromine is better, because it is more powerful and does not cause sleeplessness.

Absorption and Excretion. Caffeine is readily absorbed from the small intestine and is fully excreted in twenty-four hours. Most of it is broken down in the body by losing its methyl groups and the resultant xanthine is converted into urea. The urine contains, therefore, traces of caffeine, and larger amounts of di- and monomethylxanthine and an increase of urea. There is no increase of uric acid.

Therapeutics

Kidney. Caffeine is used as a diuretic in heart disease and nephritis. Its action is often much aided by giving digitalis at the same time. Many patients so soon become used to it, that at the end of a week it has lost its power of producing diuresis.

Nervous system. Combined with aspirin and phenacetin it is often used to alleviate headache. The function of the caffeine here is to reduce the soporific effect of the other two drugs. It is of value as an antidote to stimulate the respiratory centre in poisoning by morphine, alcohol, and other cerebral depressants.

THEOPHYLLINE

Theophyllina (B.P.). $C_7H_8O_2N_4,H_2O$. *Unoff. synonym.* Theocine.

Source. An alkaloid obtained from the dried leaves of *Camellia sinensis* or prepared synthetically.

Characters. White crystalline powder; bitter taste. Soluble in 160 parts of water.

Theophyllina cum Æthylenediamina (B.P.). *Synonym.* Aminophylline. *Tr. Names.* Cardophylin, Euphyllin.

Source. Theophylline is dissolved in ethylenediamine and evaporated to dryness.

Characters. Yellowish-white granules; faintly ammoniacal odour. Soluble in 5 parts of water.

Dose, 1½—8 gr. 0·1—0·5 G.

Preparation **(B.P.)**

Injectio Theophyllinæ cum Æthylenediamina. *Synonym.* Aminophylline Injection. Contains 0·25 G. (4 gr.) in 10 ml. (150 min.) for intravenous injection, and 0·5 G. (8 gr.) in 2 ml. (30 min.) for intramuscular injection.

Dose, 1½—8 gr. 0·1—0·5 G.—by either route.

Theophyllina et Sodii Acetas (B.P.).

Characters. White, crystalline powder. *Solubility:* 1 in 25.

Dose, 2 to 5 grs.—0·12 to 0·3 G.

THEOBROMINE

Theobromina et Sodii Salicylas (B.P.). $Na_2C_{14}H_{12}N_4O_5$. *Tr. Name.* Diuretin.

Characters. A white amorphous powder. No odour. Taste sweetish. Soluble in 1 part of water.

Dose, 10—20 gr. 0·6—1·2 G.

Action and Therapeutics

Theobromine (the chief principle in cocoa) and its isomer theophylline are more powerful diuretics than caffeine; they are efficacious in relieving œdema in diseases of the kidneys and heart. Theobromine does not act on the brain, and its use is therefore not associated with the insomnia common to caffeine. In arge doses theophylline has given rise, however, to epileptiform convulsions. Theobromine itself may be given in cachets in doses of 1 to 5 gr. (6 to 30 centigrms.). As calcium-diuretin, theobromine has been used for angina pectoris. Theophylline and sodium acetate is extensively used for cardiac œdema. Aminophylline has the action of theophylline, with much greater solubility. It is used chiefly for the prevention of **angina pectoris** and has also been employed in **coronary thrombosis.** Whether it is effective as a coronary dilator, when given by mouth, is still a moot point. Given slowly intravenously, 0·4 grm. in 10 mils of saline solution, it may certainly be efficacious if coronary spasmis, in fact, present. In the same way it may cut short **status asthmaticus,** and abolish Cheyne-Stokes respiration in heart-failure. Theophylline is used to stabilize the official injection of mersalyl. It diminishes the local irritation produced by the injection of mersalyl and aids its absorption from the muscle. It follows, therefore, that it shortens the interval between the time of injection and the start of diuresis. In therapeutic doses it is doubtful whether the xanthines have any dilator effect on the coronary arteries.

GROUP XIV

Vegetable Drugs acting chiefly on the Spinal Cord

Nux Vomica, Yohimbene and Picrotoxin

NUX VOMICA

Nux Vomica (B.P.). *Synonym.* Strychni semen. The dried, ripe seeds of *Strychnos nux-vomica.*

Composition. The chief constituents are—(1) *Strychnine,* not less than 1.2 per cent. (2) *Brucine,* which is dimethoxylstrychnine, $C_{28}H_{26}N_2O_4$, 0·9 to 1·5 per cent. Colourless prismatic crystals or pearly flakes. Very bitter, but less so than strychnine. *Solubility:* 1 in 3200 of cold water, freely in alcohol. It has the same action as strychnine, but is considerably less powerful and slower in its effects.

Nux Vomica Præparata (B.P.). *Synonym.* Nux Vomica Pulverata. Contains $\frac{1}{20}$ gr. of strychnine in 4 gr.

Dose, 1—4 gr. 60—250 mg.

Preparations (**B.P.**)

1. Extractum Nucis Vomicæ Liquidum. Alcoholic (70 per cent.). *Standardized to contain* 1·5 *per cent. of strychnine.*

Dose, 1—3 min. 0·06—0·2 ml.

2. Extractum Nucis Vomicæ Siccum. *Standardized to contain 5 per cent. of strychnine.*

Dose, $\frac{1}{4}$—1 gr. 15—60 mg.

3. Tinctura Nucis Vomicæ. *Standardized to contain* 0·125 *per cent. w/v of strychnine,* that is, 1·25 milligrms. in each millilitre, or $\frac{1}{16}$ gr. in 1 fl. dr.

Dose, 10—30 min. 0·6—2 ml.

Strychninæ Hydrochloridum (B.P.). Strychnine hydrochloride. $C_{21}H_{22}N_2O_2HCl,2H_2O$.

Characters.—Small, colourless, trimetric prisms, which readily effloresce in air; very bitter. *Solubility:* 1 in 40 water, 1 in 80 alcohol (90 per cent.).

Dose, $\frac{1}{30}$—$\frac{1}{8}$ gr. 2—8 mg.—by mouth.

Preparations (**B.P.**)

1. Injectio Strychninæ Hydrochloridi. Contains 4 mg. ($\frac{1}{16}$ gr.) in 1 ml. (15 min.).

Dose, $\frac{1}{30}$—$\frac{1}{16}$ gr. 2—4 mg.

2. Liquor Strychninæ Hydrochloridi. *Synonym.* Liquor Strychninæ. Strychnine hydrochloride, 1; alcohol (90 per cent.); distilled water. *Strength:* 1 per cent.: that is, 1 gr. in 110 ♏—1 grm. in 100 millilitres.

Dose, 3—12 min. 0·2—0·8 ml.

Action

Internal. *Gastro-intestinal tract.* Nux vomica and strychnine are intensely bitter and thus act in small doses as any other bitter in sharpening the appetite. It is a stimulant to Auerbach's plexus, but only feebly so, even in convulsant doses. In some persons therapeutic doses produce too frequent action of the bowels but not diarrhœa.

Absorption and excretion. The alkaloid and its salts are rapidly absorbed from the small intestine and circulate as such. About 20 per cent. is excreted in the urine, the remainder being destroyed in the liver. Urinary excretion takes three to five days to complete.

Spinal cord. Strychnine causes **convulsions** of spinal origin. A peripheral stimulus which would normally produce a coordinated movement involving agonists and antagonists in contraction and relaxation respectively may under strychnine cause a violent and widespread response. This effect is seen as a powerful contraction of all the skeletal muscles: there is no inhibition of antagonists. The result depends, therefore, on the relative strength of the opposing muscle groups. The extensors are the stronger and thus the limbs are outstretched and the spine hyperextended (opisthotonus). The contraction of the facial muscles gives rise to a hideous grin (*risus sardonicus*). After a few minutes the victim is cyanosed because of arrest of respiration by the tetanic spasm. The muscles thus relax, but soon another agonizing seizure appears. Two or three convulsions only are survived before death from failure of the respiratory centre closes the scene. It is believed that the precise part of the spinal cord stimulated to increased excitability by strychnine is that immediately on the afferent side of the anterior cornual cells.

When a muscle contracts, centripetal impulses go from it up afferent nerves, and these reinforce the inhibitory impulses going to the opposing muscles. Strychnine *appears* to reverse in the cord these inhibitory impulses, making them excitory. It is now known, however, that the drug merely exaggerates a normally hidden motor component in the inhibitory response. A very slight stimulus may produce a normal response, but this in itself provides a stronger stimulus and thus sets off a tetanic spasm.

Muscles and nerves. Even with enormous doses the muscles and afferent nerves are unaffected.

Brain. The motor functions of the brain are only slightly stimulated by therapeutic doses. The sensory functions of the brain are, however, heightened in activity (see *Special Senses*). Consciousness is unaffected except by terminal asphyxia. The centres in the medulla, which are really the continuation upwards of the anterior cornua of the cord, are **powerfully stimulated**, especially the **respiratory centre.** The **vaso-motor centre** is also considerably **excited,** and chiefly for this reason the blood pressure rises from the very first. The cardiac inhibitory centre is but slightly affected.

Metabolism. The great increase of muscular activity results in enormous augmentation of oxygen consumption and CO_2 output. Glycogen disappears from the liver and muscles.

Circulation. The heart is not directly affected by strychnine. The blood pressure tends to rise owing to stimulation of the vaso-constrictor centre, and blood is thus diverted from the splanchnic to the peripheral vessels. With the onset of convulsions, the blood pressure rises enormously, but falls in the intervals. The heart is, of course, accelerated at this stage.

Respiration. Respiration is rendered **quicker and deeper** because strychnine excites the spinal and medullary respiratory centres. The respiratory muscles are implicated in the general convulsions, and the patient becomes livid and ultimately asphyxiated owing to exhaustion of them, and to their prolonged contraction during the convulsive spasms. The heart continues to beat after death, which is entirely due to failure of respiration. The excessive muscular contractions occasionally cause a rise of temperature, but this is seldom great because heat-loss is much augmented owing to dilatation of peripheral vessels.

Special senses. Smell, hearing, touch, and sight are sharpened by strychnine. The field of vision, especially for blue, is enlarged. Some of these effects are probably central and others, viz., those on vision, due to local action on the peripheral sense organs.

Brucine acts like strychnine, but is forty times weaker. Methylbrucine, methylthebaine, and methylstrychnine do not influence the cord, but paralyse the ends of the motor nerves like curare. **Tolerance** is not developed for strychnine or brucine.

Therapeutics

Internal. *Gastro-intestinal tract.* Tincture of nux vomica is given as a bitter.

Circulation. Theoretically strychnine might be of value in the treatment of cardiac failure associated with vaso-motor depression, such as occurs in certain toxic states, *e.g.* pneumonia. Its action is entirely that of a vaso-motor stimulant reinforced by a similar effect on the respiratory centre.

Respiration. Strychnine may be combined with expectorants, as it stimulates the respiratory centre; and it is extremely serviceable when from any cause, such as severe bronchitis or pneumonia, the respirations are feeble and shallow; it is then best given subcutaneously in frequently repeated doses.

Nervous system. Its chief value is to increase the tone of the nervous system.

Toxicology

In about an hour after a poisonous dose the patient begins to feel uneasy from a sensation of impending suffocation. The tetanic convulsions then commence with great violence, nearly all the muscles of the body being affected at once. The limbs are thrown out, the hands are clenched, the head is jerked forwards and then bent backwards, and the whole body is perfectly stiff from the violence of the contractions. The pulse is very rapid; the temperature may rise. Hearing and sight are acute. The convulsion lasts a minute or two, then the muscles relax, and the patient feels exhausted and sweats all over. The intermission is short, convulsions soon come on again, and again there is a relapse to the state of muscular relaxation. The convulsions now rapidly increase in severity, and owing to the violent contractions of the muscles of the back, the patient is in the position of opisthotonos, resting on his head and his heels. The abdominal muscles are as hard as a board, the chest is fixed, the face becomes livid, the eyeballs are staring. The contraction of the muscles of the face causes a risus sardonicus; but those of the jaw are not affected till quite the end. Consciousness is retained to the last. The slightest noise or even a bright light will reflexly bring on the convulsions, which may jerk the patient out of bed. Ultimately he dies from exhaustion and asphyxia. The smallest dose of strychnine known to have killed is half a grain. *Post mortem.* The usual appearances of death by asphyxia are seen.

Strychnine poisoning is liable to be confounded with *tetanus*, but in this disease symptoms come on more slowly, the muscles of the jaw are implicated very early, and there is continuous muscular rigidity with paroxysmal exacerbations, but never complete muscular relaxation.

Treatment. Both chloroform and avertin will prevent the spasms, but the danger is that they depress yet further an exhausted respiratory centre. Wash out the stomach with strong tea to form the insoluble tannate. This compound is easily broken up and must be eliminated. Inject intravenously sodium amytal (10 grs.), or sodium phenobarbitone (7 grs.). With depression of the respiratory centre, use artificial respiration: the chances of recovery by now are almost negligible, particularly in view of the slow excretion.

Antagonism

In a sense strychnine is antidotal to chloral and morphine, but it is not a strict antidote, for they act chiefly on the cerebrum. Still, chloral is valuable in strychnine poisoning, and although the antagonism with Calabar bean and gelsemium is more accurate, as both depress the anterior cornua, yet they are of very little use in strychnine poisoning.

Yohimbine (Quebrachine).
SOURCE. An alkaloid prepared from the bark of an African tree (*Corynanthe johimbe*).
CHARACTERS. White acicular crystals.

Preparation (B.P.C.)

Yohimbinæ Hydrochloridum.
Dose, $\frac{1}{20}$—$\frac{1}{8}$ gr. 0·003—0·008 G.

Action and Therapeutics

Stimulates and in large quantities paralyses the medullary centres and cord. Within ten minutes of the injection of 0·015 grm. penile erection occurs and is maintained for five to ten minutes. In twenty to thirty minutes trembling, headache, and considerable rise of blood pressure are produced. These effects pass off in about the same length of time. Larger doses produce extreme nausea but not vomiting. Respiration at first rapid, then slow and weak.

Small quantities dilate vessels of skin and those of genital organs. This in conjunction with hyperæmia of lumbar cord accounts for its use as an aphrodisiac in man and cattle.

PICROTOXIN

Picrotoxinum (B.P.). *Synonym.* Cocculin. $C_{30}H_{34}O_{13}$. A glycoside obtained from Anamirta paniculata.
CHARACTERS. Bitter, colourless crystals. *Solubility.* 1 in 334 of water; 1 in 13 of alcohol.
Dose, $\frac{1}{100}$—$\frac{1}{20}$ gr. 0·6—3 mg.

Preparation (B.P.)

Injectio Picrotoxini. Contains 3 mg. ($\frac{1}{20}$ gr.) in 1 ml. (15 min.).

Dose, as for picrotoxin by intramuscular or intravenous injection.

Action

Picrotoxin is a convulsive poison exerting a stimulant effect on the central nervous system. In man this is chiefly on the mid-brain and medulla, but the cortex is undoubtedly stimulated and in higher mammals this action is largely responsible for the clonic convulsions. They are altered in character with ablation of the cortex and disappear on section below the pons.

Stimulation of the medullary centres produces vomiting and the usual effects on respiration, blood pressure, and pulse-rate, but they are not elicited except by convulsive doses. Picrotoxin has a remarkable power of combating the cerebral depression of barbiturates, chlorbutol, paraldehyde and tribromoethyl alcohol. On the other hand it is ineffective in abolishing alcoholic depression. The stimulation of the respiration is well-marked in sub-convulsive doses when the centre is already depressed by the drugs mentioned. It has been suggested that this is not a direct action on the medulla but an indirect one by reduction of narcosis. In depression of the respiration by morphine, although picrotoxin will show a stimulant effect which may be beneficial, there is a risk that the combined stimulation of the cord by morphine added to that of picrotoxin on the brain may give rise to convulsions. Death is due to respiratory failure.

Excretion. Picrotoxin is rapidly destroyed in the body and only traces are found in the urine.

Therapeutics

Picrotoxin is given for **barbiturate, paraldehyde** and **bromethol poisoning** in doses of $\frac{1}{6}$ gr. intramuscularly or intravenously half-hourly until muscular twitching occurs. Large doses can be tolerated in barbiturate poisoning.

GROUP XV

Drugs acting chiefly on Autonomic Ganglia and Nerve Endings

Conium, Gelsemium, Nicotine, Curara, Cocaine, Cocaine Substitutes, Aconite, Veratrine, Pilocarpine, Carbachol and Physostigmine.

CONIUM

Conii Folium (B.P.C.). *Synonym.* Hemlock Leaf. The fresh leaves and young branches of *Conium maculatum.*

COMPOSITION. The chief constituent is—(1) *Coniine,* $C_8H_{16}HN$, propyl piperidine, the active principle.

Dose, 2—8 gr. 0·12—0·5 G.

Action

EXTERNAL. Coniine has no influence on the unbroken skin.

INTERNAL. *Gastro-intestinal tract.* It may occasionally give rise to vomiting and diarrhœa, for it stimulates and then paralyses all sympathetic ganglia like nicotine.

Circulation. Coniine is absorbed into the blood, and circulates unchanged. It causes vacuoles to appear in the red cells. It stimulates and then depresses the cardiac vagal ganglia, and hence the pulse slows and then becomes rapid. The blood pressure rises at first and then falls, owing to the same action in the ganglia of the vaso-constrictor nerves.

Respiration. Owing to the profound paralysis of the respiratory motor nerve endings, and the later depression of the respiratory centre, death takes place from enfeeblement of respiration and consequent **asphyxia.**

Nervous system. Nerves. Coniine powerfully **depresses the periphery of all the motor nerves,** and in moderate doses only affects those to striped muscle. This leads to paralysis of all the muscles of the body, but they themselves are unaffected, retaining their irritability to local stimuli. The motor nerve trunks and the sensory nerves are not implicated unless the dose is very large ; then their conducting power is impaired. The effects on nerves are well illustrated in the death of Socrates, for he was directed to walk about till his legs felt heavy (motor paralysis), and later, when his foot was pressed he could not feel.

Spinal cord. This remains uninfluenced till quite late ; then, if poisonous doses of conium have been given, the motor cornua are feebly depressed, as is also the respiratory centre in the medulla. These actions are probably due to the methylconiine. As the amount of this is variable in different specimens, the exact period at which these effects come on varies with different preparations. In some animals asphyxial convulsions are very marked.

Brain. Except for the respiratory centre, where the action is probably slight, the whole of the brain is unaffected by coniine. Consciousness is preserved until the stage of asphyxia.

Eye. Coniine, dropped into the eye, causes contraction of the pupil reflexly from the conjunctival irritation. But soon the pupil dilates, and accommodation is paralysed; the same usually happens when the drug is given internally. Probably these results are owing to paralysis of the terminal portions of the third nerve, for well-marked **ptosis,** which is due to this cause, is present, but the pupillary effects are partly due to depression of the ciliary ganglion, as coniine paralyses all peripheral ganglia.

Coniine is rapidly excreted unchanged, chiefly in the urine.

Therapeutics

Conium is rarely given as a medicine. It has been given in spasmodic diseases, as whooping-cough, in chorea, tetanus, asthma, and epilepsy, but in all it does little or no good.

Toxicology

The symptoms produced by a poisonous dose are in strict accordance with the physiological action. The sufferer feels his legs to be heavy; on attempting to walk he staggers, and finds he can hardly move them, and finally he has to lie down because he has no power over them. The arms become powerless, and lie motionless at his side. There is ptosis, and dimness of vision from paralysis of accommodation; the eyes are fixed, the pupil is dilated. Swallowing becomes difficult. Respiration is laboured, the voice is lost, and death takes place from asphyxia. *Post mortem.* The organs are found congested with venous blood.

Treatment. Emetics and wash out the stomach. Give tannic acid and again wash it out. Stimulants subcutaneously. Warmth to the feet. Artificial respiration should be carried out thoroughly because the poison is rapidly excreted.

GELSEMIUM

Gelsemium (B.P.C.). *Synonyms.* Gelsemii Radix; Yellow Jasmine. The dried rhizome and root of *Gelsemium sempervirens.*

COMPOSITION. The chief constituents are—(1) Gelsemine, a very poisonous alkaloid, existing as yellowish-white minute crystals. (2) Gelseminine, a yellow-brown, bitter substance.

Dose, $\frac{1}{4}$—1 gr. 0·016—0·06 G.

Preparation (B.P.C.)

Tinctura Gelsemii. Gelsemium, 1; alcohol (60 per cent.), 10.

Dose, 5—15 min. 0·3—1 ml.

Action

EXTERNAL. None.

INTERNAL. Gelsemium produces no effect on the stomach or intestines. Its powerful general physiological effects are due to the gelsemine in it. Its mode of action is that of coniine.

Therapeutics

Gelsemium being an uncertain, very powerful poison, is not often prescribed, but sometimes it is used successfully for neuralgia and migraine. Its mode of action here is not known. It should be given in small quantities hourly and discontinued if dizziness, dilatation of the pupil, double vision or dropped lids arises. Its effect is uncertain and its use steadily diminishing. Discs, each containing $\frac{1}{500}$ gr. (0·1 milligrm.) gelsemine, are made for application to the eye from which it is absorbed.

NICOTINE

Tabacum (B.P.C.). Tobacco Leaves. The dried leaves of *Nicotiana Tabacum.*

Composition. The chief constituents are—(1) *Nicotine* $C_{10}H_{14}N_2$ (2 to 8 per cent.). A colourless, volatile, oily alkaloid, smelling and tasting like tobacco leaves, darkening with age. Soluble in water, more so in alcohol and ether. Turkish tobacco contains hardly any. (2) Nicotianin. (3) Salts and flavouring agents.

Nicotine is the main and most active constituent of tobacco smoke. Pyridine bases are present, but not in sufficient quantity to produce any effect, except to exert an irritant action on the gastric mucosa.

Action

Tobacco leaves act in virtue of their nicotine, one of the **most powerful and rapid poisons** known.

External. Nicotine is a powerful antiseptic.

Internal. *Gastro-intestinal tract.* Nicotine in even minute doses ($\frac{1}{7}$ gr., 10 mgm.) promptly produces greatly increased salivary flow, due to action on the salivary ganglionic apparatus, burning pain in the mouth, œsophagus, and stomach, horrible nausea, quickly succeeded—owing to its action on the ganglia of the gastro-intestinal muscle—by vomiting and free purging accompanied by **extreme collapse.** There is then present a rapid, very feeble pulse, intense muscular weakness, laborious respiration, partial loss of consciousness, occasional convulsions, icy extremities, and profound general collapse. A dose of nicotine may kill in three minutes, but in both man and animals a certain tolerance may be acquired.

Circulation. Nicotine stimulates and then paralyses all the autonomic ganglia. Its effect on the circulation must therefore depend upon the resultant of this action on the vagal and sympathetic (accelerator) ganglia. In addition there is evidence of slight stimulation of the vagal centre and direct depression of the heart muscle. Actually the pulse is usually slowed at first, then becomes rapid, and in profound poisoning it eventually develops a slow, irregular and feeble beat.

Respiration. This is at first accelerated and deepened ; ultimately it is **paralysed** from depression of the centre. Death is due to this. The bronchi, after transient constriction, dilate. This is due to stimulation of the vagal and sympathetic ganglia, the last soon predominating.

Nervous system. The higher faculties are depressed by large doses, for those poisoned become comatose within even a minute or two of taking a large dose. Nicotine produces fibrillary twitching and slow, prolonged, contraction of frogs' muscle. This action is antagonized by curara and is exerted at the myoneural junction. The convulsions occasionally observed in man, and always in the frog, are probably due to spinal stimulation. Ultimately the **function of the myoneural junction of motor nerves is entirely abolished** after initial stimulation, hence intense muscular weakness. Probably the sensory nerves, and certainly the muscles, escape.

Whether injected into the circulation or applied locally to nerve ganglia, nicotine paralyses them after a brief period of stimulation, and to this many of its actions, *e.g.* gastro-intestinal, are due. After internal administration or local application of nicotine the superior cervical ganglion, for example, is paralysed, so that while post-ganglionic stimulation causes blanching of ear, dilatation of pupil and secretion of saliva, pre-ganglionic has no effect.

Eye. A toxic dose taken internally, or the local application of nicotine to the eye, **contracts** the **pupil** of man and most animals. This will occur in excised eyes, and is therefore a local effect. With some animals nicotine is a mydriatic. The effect depends upon the balance of action in the ciliary and superior cervical ganglia.

Secretion. Nicotine first stimulates but ultimately paralyses the secretory structures of the salivary, sweat, lachrymal, and probably all other glands. It acts on the ganglionic apparatus.

Elimination. Nicotine is eliminated partly by the lungs, but chiefly in the urine.

Therapeutics

Nicotine is not used therapeutically. Formerly tobacco was employed in the treatment of asthma to induce relaxation of the bronchioles. For this purpose it was necessary to smoke until profound nausea was induced.

Tobacco-smoking, in those who are unaccustomed to it, produces, to a greater or less degree, the symptoms of gastro-intestinal irritation and collapse just mentioned. Even in those who are used to it the smoke may produce catarrh of the pharynx. Moderate smoking raises the blood pressure by vaso-motor constriction and quickens the pulse and respiration, and after breakfast assists the daily action of the bowels. After excessive smoking the vaso-motor centre is depressed, the blood pressure falls, and there is general collapse. With many people smoking has an obscure effect, especially among those who lead sedentary lives, in stimulating the brain and producing a peaceable, calm state of mind. Carboxy-hæmoglobin up to not more than 5 per cent. is produced in all regular smokers and is not responsible for the "short-windedness" induced. Over-indulgence in it may lead to loss of appetite, irregularity of the heart, chronic laryngeal and pharyngeal catarrh, and retrobulbar neuritis of the optic nerve. The effect of this is that the sufferer complains that objects look misty, he has a central scotoma, sometimes complete. often only for red and green, and finally atrophy of his optic nerve.

The pharyngitis, chronic cough, and gastritis and probably tobacco amblyopia are due to the intensely irritating pyridine bases, collidine and lutidine.

The nicotine contained in one cigar represents twice the fatal dose (70 mgm.) if given intravenously.

The pituri plant contains an alkaloid, piturine, acting exactly like nicotine. The leaves of it are used in Australia instead of tobacco.

CURARE

Curara (B.P.C.). *Synonyms.* Ourari, Urari, Woorara, Woorali. The South American arrow poison, prepared from the bark of *Strychnos toxifera* and other species of Strychnos.

Characters. A blackish-brown, dry, bitter extract.

Composition. The active principles of curare are alkaloids which differ in each variety of the crude drug. These varieties are named according to the form of container in which they are supplied : thus curare in bamboo tubes is *tubocurare ;* that in jars is *pot curare ;* and that supplied in gourds is *calabash curare.* Tubocurarine is the most important alkaloid obtained from the first, and it is now the chief curarine employed as an adjunct to anæsthesia. The calabash form yields the most potent alkaloid, whilst pot curare contains three alkaloids of which protocurarine has the typical curare action. The difficulty of tracing the source and method of extraction in the past, combined with the technical difficulties of extracting and separating the alkaloids, has prevented the use of curare in therapeutics until 1942. Now purified preparations are available. One sold under the name of *Intocostrin* is a purified fluid extract obtained from *Chondodendron tomentosum* (Amazon). It is standardized physiologically to contain 20 units, or 20 mgm. of curare extract, per mil.

On the other hand the dose of *d*-tubocurarine (curarine chloride) is given by weight. In man 1 unit of Intocostrin is of the potency of 0·3 mgm. of *d*-tubocurarine chloride.

Dose. Intocostrin 1·2 mg.
Tubocurarine 0·4 mg. } per kilo of body-weight by intravenous injection, repeated when necessary.

Action

Curare acts by blocking nerve impulses where they are transmitted by acetylcholine in autonomic ganglia and muscle, but not on postganglionic fibres. Thus all skeletal muscles are paralysed, and also there is blockage of synaptic transmission between pre- and postganglionic fibres of the sympathetic nervous system. In fact it blocks the " nicotine effect " of acetylcholine. The action of curare on muscle and nerve cell is a direct one rendering the cell irresponsive to the chemical mediator. There is no general paralysing action on these structures which will, in fact, respond normally to other forms of stimuli during curare action. Thus direct electrical stimulation will excite muscle to contract, and nerve impulses can be discharged from curarized ganglia by the application of potassium salts.

Physostigmine and prostigmine antagonize the action of curare. Approximately one part of prostigmine will counteract the effect of five parts of tubocurarine.

Curare seems to exert a selective action on certain muscles, for quite a small dose of tubocurarine intravenously, *e.g.* 10 mgm., causes diplopia and ptosis whilst the limbs are unaffected. Twice this amount produces within 2 minutes strabismus, ptosis, general weakness, paralysis of muscles of face and neck which spreads to larynx, limbs, abdominal muscles, and intercostals in that order. Swallowing and coughing are not affected by this dose. Within 15 minutes the power begins to return in the reverse order.

A dose of 30 mgm. intravenously causes complete paralysis of all striped muscle including the intercostals. Diaphragmatic movement is not quite lost but is irregular and slow. Consciousness is unimpaired at first but with virtual cessation of respiration it is lost owing to asphyxia. Artificial respiration, preferably by means of the breathing bag of the anæsthetic apparatus, is highly effective and may be maintained until the effect of curare begins to pass off, which is usually seen in 20 minutes, or sooner if prostigmine be injected.

The effects of curare obtained after intramuscular injection are similar though less intense and of longer duration as compared with the same amount intravenously.

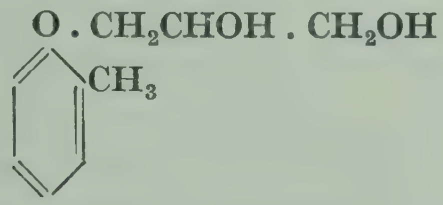
Absorption and Excretion. Curare is probably partly destroyed in the alimentary tract. It has no action when taken by mouth. The main reason for this is that absorption from the gut is slower than is excretion by the kidneys. The drug is rapidly eliminated in this way and very little remains in the body within half-an-hour of administration intravenously. Some curare is destroyed in the liver.

Uses

Curare in the form of Intocostrin or Tubocurarine is extensively used as an adjunct to anæsthesia. Premedication with atropine or hyoscine is customary. Its value lies in the muscular relaxation it produces and it is thus employed chiefly in abdominal surgery. It is usual to induce anæsthesia with a basal narcotic, notably thiopentone, and to follow this with tubocurarine intravenously. Gas-and-oxygen administration is then sufficient to maintain adequate anæsthesia. Alternatively cyclopropane and curare form an excellent combination. Both thiopentone and curare can be repeated at suitable intervals during the course of the operation. The preliminary intravenous dose of curare may be followed by intramuscular injection 40 minutes later when the effects of the first dose are beginning to wear off.

Curare has been given with success in tetanus in order to prevent the muscular spasms.

Myanesin. This is the trade name for β-dihydroxy-γ-(2-methylphenoxy)-propane, a synthetic glycerol ether.



Characters. Colourless, odourless, crystalline. Neutra reaction. Solubility: 1 in 100 water, greatly increased by the addition of urea: freely in alcohol. Solutions are stable and can be sterilized by heat.

Dose (provisional). **20 mg. per kilo** of bodyweight—intravenously.

Action and Uses

Myanesin has a depressant action on the spinal cord thus producing muscular relaxation and, with larger doses, paralysis. It antagonizes drugs causing spinal convulsions, *e.g.* strychnine. It has also some depressant action on the brain and may cause a sense of confusion, ataxia and nystagmus.

It is quickly destroyed in the body and has a high therapeutic index. Therapeutic doses have no effect on respiration or blood pressure. It may cause hæmoglobinæmia. It is more effective when given by intravenous injection than by mouth. It relieves for about one hour the spasticity of hemiplegia. Its effects in the rigidity of Parkinsonism are very variable.

It is used in conjunction with barbiturate and other anæsthetics to produce muscular relaxation.

COCAINE

Cocaina (B.P.). $C_{17}H_{21}O_4N$.

Source. An alkaloid obtained from Coca (Erythroxylum Coca) leaves and its varieties.

Characters. Colourless monoclinic prisms with a slightly bitter taste followed by numbness. *Solubility:* Almost insoluble in water. 1 in 10 alcohol (90 per cent.); 1 in 4 ether; 2 in 1 chloroform; 1 in 4 oleic acid; 1 in 12 olive oil.

Preparation (B.P.C.)

Unguentum Cocainæ. Cocaine, 1; oleic acid, 4: prepared lard, 20. *Strength:* Contains 5 per cent. of cocaine.

Cocainæ Hydrochloridum (B.P.). Cocaine Hydrochloride. $C_{17}H_{21}O_4N, HCl$.

CHARACTERS. Colourless acicular crystals or a crystalline powder. *Solubility:* 2 in 1 of water, 1 in 3 of alcohol (90 per cent.), 1 in 3 of glycerin.

Dose, $\frac{1}{8}$—$\frac{1}{4}$ gr. 8—16 mg.

Preparations (B.P.)

1. **Oculentum Cocainæ.** 0·25 per cent. of cocaine hydrochloride.

2. **Lamella Cocainæ.** Discs of gelatin and glycerin containing cocaine hydrochloride $\frac{1}{50}$ gr. (1·3 mg.).

3. **Trochiscus Krameriæ et Cocainæ.** Each contains extract of krameria 1 gr. (60 mg.), cocaine hydrochloride $\frac{1}{20}$ gr. (3 mg.).

4. **Suppositoria Cocainæ.** Contains 15 mg. ($\frac{1}{4}$ gr.).

Action

Local. Cocaine has little action on the unbroken skin, but if injected subcutaneously or applied to mucous membranes—as, for example, those of the eye, nose, mouth, rectum, vagina—it produces **complete local anæsthesia** to pain and touch, by action on nerve fibrils, so that small operations can be performed without the patient feeling them. Applied to the nose or tongue cocaine abolishes smell and taste (especially for bitter substances) respectively. A 5 or 10 per cent. solution of the hydrochloride is strong enough to paralyse the sensory nerves. Insensibility to touch and pain is produced by weaker solutions (*e.g.* 0·5 per cent.) than those needed to abolish thermal sensation and the passage of motor impulses. If a 2 per cent. solution is injected into the subdural space, sensation—and with larger doses motion—is abolished in the parts supplied by the nerves with which it comes in contact. Local application causes blanching of the area treated owing to contraction of the blood vessels.

This is probably due to a direct action on the vessel walls.

Eye. When a solution of cocaine of about 4 per cent. is dropped into the eye local anæsthesia is produced first of the conjunctiva and cornea, later of the iris. It is attained in about seven minutes, and lasts about thirty minutes. At first there may be a transitory contraction of the pupil. This is probably due to reflex action, and soon it gives way to **dilatation.** The maximum is attained in an hour or two. The normal state is regained in from twelve to twenty-four hours. The dilated pupil is feebly responsive to light, and the dilatation is rapidly overcome by physostigmine and pilocarpine and can be augmented by the instillation of atropine. The ocular tension is usually lowered on account of vascular construction. Accommodation is partially, but never completely, paralysed. These effects are due to its sympathomimetic action in preventing the destruction of adrenaline or sympathin. All these effects are slowly produced if large doses of cocaine are taken internally.

Internal. *Gastro-intestinal tract.* Large doses may lead to diarrhœa from muscular stimulation. Larger doses paralyse the gut.

Circulation. Large doses stimulate both the accelerator centre and the cardiac muscle, and therefore the pulse quickens, and as the vaso-motor centre is stimulated the blood pressure rises. Subsequently the heart muscle is poisoned and the heart becomes slow and feeble. Death may be due to this effect.

Respiration. Cocaine acts upon the respiratory centre, first stimulating it, so that the rapidity and depth of respiration are increased ; but soon depression of the centre follows, the respiratory movements become feeble, of the Cheyne-Stokes type, and death takes place from **asphyxia.**

Nervous system. Cerebrum. Cocaine is a **direct stimulant** to the central nervous system, affecting first the higher centres, later the cord. Subsequent to stimulation depression follows. Paralysis of the sensory nerve endings does not occur when cocaine is circulating, because in order to produce this effect the concentration in the blood would greatly exceed that necessary to paralyse the central nervous system. Moderate doses greatly **increase the bodily and mental power,** and give a sense of calm and happiness with abolition of bodily and mental fatigue. This greater physical energy renders possible the performance of long, exhausting muscular feats. For these effects, coca leaves mixed with clay or ashes are chewed by thousands of the inhabitants of Peru and the neighbouring countries. A single large dose causes mental excitement, delirium, and convulsions, due to a descending stimulation of the central nervous system. An excessive indulgence in the habit of coca chewing leads to indigestion, extreme emaciation, insomnia, and enfeeblement of intellect. Increase of sexual desire or sexual perversion is often accompanied by impotence.

Sympathetic Nervous System. Cocaine potentiates adrenaline and sympathin effects arising from sympathetic nerve stimulation. It does this by preventing amine oxidase from destroying adrenaline (or sympathin) at the nerve-endings.

Temperature. This may rise in cocaine poisoning by 6 to 8° Fahr., owing to cerebral action, increased muscular activity, and vaso-constriction.

Excretion. Cocaine is partly excreted by the kidneys. In dogs the drug is mainly destroyed in the tissues, only about 5 per cent. appearing in the urine.

Therapeutics

Local. Cocaine is no longer used extensively as a local anæsthetic because of its toxicity and tendency to produce habit formation. It has been largely superseded by various substitutes, *e.g.* procaine, which do not induce addiction. Its power of penetrating mucous surfaces makes it, however, an ideal anæsthetic for use in the nose, throat, urethra and anal canal. Vaso-constriction induced by cocaine is likewise of great value, particularly in the nose, for the consequent shrinkage of the mucous membrane improves visibility and access to the passages and assists sinus drainage.

Its action is enhanced and prolonged by the addition of one minim of the official adrenalin liquor to each 20 minims of cocaine used.

The strength of cocaine solution should be varied according to its use. Cocaine 0·5 grm. in castor oil 95 grm. forms a useful application to the eye irritated by a foreign body. This is not included in the D.D.A. Relief of pain can be secured by 2 per cent. whilst complete anæsthesia needs 5 per cent. Up to 10 per cent. solutions may be needed for full anæsthetization of the larynx and for operations on the eye.

General. Cocaine is not used in Europe for its restorative effects. Severe poisoning symptoms are rarely noticed unless it is injected. Then it may quickly cause vertigo, pallor, fainting, profound cardiac and respiratory depression with tremors and other nervous symptoms which may in very rare instances persist for months, even if the other symptoms are overcome.

Chronic cocaine poisoning. Synonym, Cocamania. The sufferer takes cocaine either for its pleasant effects or because he thinks it will help him to break himself of the morphine habit, or he takes it with morphine. It is usually administered by sniffing up the nose. The pulse is rapid, and fainting is common. There is much wasting and the patient looks pale and death-like. Usually he suffers from insomnia and he may become acutely maniacal with delusions of persecution. Visual and other hallucinations are often present, and it is very characteristic that patients complain of little animals creeping on the skin, "cocaine bugs," they say. As a result of the cerebral stimulation, they are extraordinarily prolix in both conversation and writing. Large quantities of the leaves are chewed by some of the inhabitants of South America.

COCAINE SUBSTITUTES

Benzocaina (B.P.). *Synonym.* Ethyl Aminobenzoate. *Tr. Name.* Anæsthesine.

CHARACTERS. White, crystalline powder, soluble in 2500 of water and 8 of alcohol.

Dose (not official), **5—10 gr. 0·3—0·6 G.**

Therapeutics

A cocaine substitute extensively used as 2 per cent. in olive oil in nasal disease, and hay fever and, in ointment form (10 per cent.), for hæmorrhoids, eczema, and intertrigo. It is contained in a proprietary preparation A.B.A., now known as Proctocaine, which is injected locally for fissure *in ano.* Owing to its insolubility it is convenient for dusting on mucous surfaces.

Orthocaina (B.P.). *Tr. Name.* Orthoform.

CHARACTERS. A white powder, sparingly soluble in water, soluble in 7 parts of alcohol.

Dose (not official), **1½—3 gr. 0·1—0·2 G.**

Therapeutics

Similar to those of benzocaine.

Cinchocainæ Hydrochloridum (B.P.). White hygroscopic crystals soluble in water and alcohol.

Therapeutics

A useful local anæsthetic.

Butacainæ Sulphas (B.P.). A white crystalline powder, slowly soluble in water.

Therapeutics

Valuable for surface anæsthesia as it penetrates mucous membranes.

Butylis Aminobenzoas (B.P.). A white crystalline powder, soluble in dilute acids, alcohol, and ether. It is hydrolysed on boiling with water.

Therapeutics

A rapidly acting local anæsthetic for use on mucous surfaces. Its action is more prolonged than that of butacaine.

Procainæ Hydrochloridum (B.P.). *Synonym.* Ethocaine Hydrochloride. *Tr. Name.* Novocain.

CHARACTERS. White, crystalline powder, freely soluble in water.

Dose (not official), **½—2 gr. 0·03—0·12 G.**
Up to 15 gr.—up to 1 G.—by subcutaneous injection.
Up to 2½ gr.—up to 0·15 G.—by intrathecal injection.

Preparations (B.P.)

1. **Injectio Procainæ et Adrenalinæ Fortis.** Contains 2 per cent. of procaine hydrochloride and 0·1 per cent. of chlorocresol.

2. **Injectio Procainæ et Adrenalinæ Mitis.** Contains 0·5 per cent. procaine hydrocloride.

Dose (not official), **up to 10½ fl. ozs.—up to 300 ml.**—for infiltration anæsthesia.

Action and Therapeutics

Absorption from mucous membranes is slight and, therefore, it is ten times weaker as a surface anæsthetic than cocaine. It has no effect upon the pupil or the blood vessels. Extensively used for infiltration anæsthesia in preference to cocaine because of its lower toxicity. Procaine is safer than most of the cocaine substitutes.

Amethocainæ Hydrochloridum (B.P.). *Synonym.* Tetracaine Hydrochloride. *Tr. Names.* Decicain, Anethaine.

CHARACTERS. White crystalline powder, soluble in water. A local anæsthetic of the procaine series used in 2 per cent. solution for surface anæsthesia. Should be combined with adrenaline to minimize toxic reactions. Used especially in preparation for gastroscopy.

Preparation (**B.P.**)

Injectio Amethocainæ Hydrochloridi. *Synonym.* Injection of Tetracaine Hydrochloride.

Dose, according to label.

Percaine. A trade name for the hydrochloride of α-buty oxycinchoninic acid diethylethylendiamide.

A local anæsthetic which has achieved great popularity. The solutions can be sterilized by boiling, but should be kept in alkali-free glass to avoid separation of the base.

Anæsthesia is obtained by concentrations ten times less than that required for cocaine, whilst the action is considerably longer. A 0·1 per cent. solution is used for infiltration and spinal anæsthesia. The toxicity of percaine is less than that of cocaine, but exact figures on this point are still lacking. Deaths have followed its use for spinal anæsthesia.

The symptoms of poisoning, viz. clonic convulsions, motor excitement, acceleration of respiration and ultimate paralysis point to an action similar to that of cocaine on the central nervous system.

Novutox. A trade preparation of para-aminobenzoyl-diethyl-aminoethanol hydrochloride and adrenalin in Ringer's solution. Certain quinine derivatives are added.

Dose, 1 to 2 mls. by injection of a 2 per cent. solution.

Action and Therapeutics

Novutox is a proprietary cocaine substitute issued in 2 per cent. solution. It is stable and antiseptic and is, therefore, of especial value for dental anæsthesia because it can be injected into infected areas. It is readily diffusible and produces complete local anæsthesia.

ACONITE

Aconitum (**B.P.**). Aconite Root. The dried root of *Aconitum napellus.* Monkshood

COMPOSITION. The chief active principle is the alkaloid *aconitine.*

Preparation (B.P.)

Linimentum Aconiti. Powdered root, 500; camphor, q.s.; alcohol (90 per cent.), q.s. *Strength* · 0·2 per cent. or 0·2 G. in 100 ml.

Aconitina (B.P.C.). Aconitine $C_{34}H_{47}NO_{11}$.

SOURCE. An alkaloid obtained from aconite root.

CHARACTERS. Colourless, hexagonal prisms of the rhombic system. Melting-point, 198° C. Its salts are crystalline. By partial hydrolysis aconitine forms benzaconine, and on further hydrolysis it forms aconine and benzoic acid. *Solubility:* Readily in alcohol and chloroform, less so in ether; nearly insoluble in water.

Dose, $\frac{1}{640}$ gr.—0·0001 G.

Preparation (B.P.C.).

Unguentum Aconitinæ. Aconitine, 1; oleic acid, 8; prepared lard, 41.

Action

The action of aconite is due chiefly to the aconitine in it, and therefore they may be considered together.

EXTERNAL. Applied to the skin, to a mucous membrane, or to a raw surface, aconitine first stimulates and then paralyses the sensory nerves; it thus causes first **tingling**, then **numbness and local anæsthesia** for touch, pain, and temperature, which last some time. Unless the skin is sound a dangerous quantity may be absorbed. It is intensely irritant to the nostrils, causing, when it is inhaled, sneezing and much secretion with an icy cold sensation.

INTERNAL. *Alimentary tract.* Numbness and tingling are produced in the mouth and a greatly increased flow of saliva. Its bitter taste is that common to all alkaloids, but taste sensation is not otherwise affected until after absorption. It is then blunted in the same way as other forms of sensation. There are no other gastro-intestinal symptoms, provided the dose is not very large; if it is, there may be vomiting and purging.

Heart. With small doses the heart is unaffected. In larger quantities the pulse rate is quickened on account of the nausea arising from irritation of the stomach. If more is given the force becomes less, and the pulse is slowed from stimulation of the vagus centre. After large doses the irritability of the myocardium is increased, giving rise to extra-systoles and not infrequently reversal of heart beat, *i.e.* ventricular contraction precedes that of the auricles and conditions the rate. The conductivity is lessened, and contractility impaired with the production of pulsus alternans. By this time the heart beat is very rapid. As the irregularity and frequency of ventricular contractions increase, the blood pressure rapidly undergoes great variations. The ventricles, always more affected than the auricles, pass into a condition of fibrillation. Moderate doses lead to a fall of blood pressure, almost entirely secondary to the action on the heart or its nerves. The vaso-motor centre is eventually paralysed.

Respiration. This, after a transitory quickening, is steadied and slowed, expiration being considerably prolonged. The movements become more slow and dyspnœal, the respiratory centre is then powerfully depressed, and is usually paralysed immediately before the onset of ventricular fibrillation.

Nervous system. It appears clear that aconite, whether given internally or applied locally, depresses the activity of the peripheral terminations of the nerves; the nerves of common sensation and temperature are affected long before the motor. Any pain that may be present is relieved. Large doses in man cause clonic convulsions, possibly the result of stimulation of the lower motor centres, but probably the outcome of asphyxia. There is initial stimulation of the vaso-constrictor and cardio-inhibitory centres, followed by paralysis. The respiratory centre is depressed from the outset. The pupil dilates terminally owing to convulsions and asphyxia. Later on the paralysis of the motor nerves gives rise to muscular weakness. It is doubtful whether the cord is influenced.

Temperature. Aconite causes a febrile temperature to fall owing to decreased sensitivity of the thermal regulating centres.

Skin. Aconite is a mild diaphoretic. Occasionally it produces an erythematous rash.

Excretion. Aconitine is excreted in the urine.

Benzaconine is bitter, and does not cause tingling or numbness of mucous surfaces; in large doses it slows the pulse beat very strikingly because the auricular beats are frequently not followed by ventricular contraction. Its action is probably chiefly on the heart muscle itself. It does not paralyse sensory nerves, but greatly interferes with motor nerves and causes a semi-comatose condition. It will be noticed that it is in almost all respects contrary in action to aconitine.

Aconine is bitter, but does not produce numbness. It is non-toxic as regards the heart, and opposes the cardiac inco-ordination and asequence caused by aconitine. It depresses motor nerves and respiration very strikingly, probably acting like curare.

Therapeutics

External. As aconite produces local anæsthesia, it has been applied externally and often with great benefit in cases of neuralgia, especially facial neuralgia. A small piece of the ointment may be rubbed in till numbness is produced, but as this is a very expensive preparation it is usually better to paint on the liniment with a camel's hair brush. Aconite should never be used externally unless the skin is quite sound.

Internal. Aconite has been given internally for neuralgia, but it has no effect unless used in dangerously large doses. It is not used internally so much as formerly, when it was administered in almost every febrile disease, with the object of decreasing the force and tension of the pulse. Critical observation has shown that this effect is not produced by therapeutic doses with any regularity.

Aconite is the most poisonous of all alkaloids, symptoms occurring after taking $\frac{1}{300}$ gr. by mouth. Subcutaneous injection is very painful.

Toxicology

The symptoms come on quickly; in a few minutes there is a severe burning, tingling sensation in the mouth, followed by numbness. Vomiting begins in an hour or so, and is very severe. There is an intense abdominal burning sensation. The skin is cold and clammy. Numbness and tingling with a sense of formication of the whole skin trouble the patient very much. The pupils are dilated, the eyes fixed and staring. The muscles become very feeble, hence he staggers. The pulse is small, weak, and irregular. There is difficulty of respiration. Death takes place from asphyxia, or in some cases from syncope. The patient is often conscious to the last. *Post mortem.* The usual signs of death from asphyxia are seen.

Treatment. Wash out the stomach promptly; give emetics. Use artificial respiration early. Inject stimulants, as ether or atropine. Hot blankets and bottles.

VERATRINE

Veratrina (B.P.C.). Veratrine, a mixture of alkaloids obtained from sabadilla, the dried ripe seeds of *Schœnocaulon officinale*. It usually consists of cevadine, cevadilline, sabadine, and cevine.

Source. Prepared from cevadilla seeds by exhaustion with alcohol.

Characters. A pale grey amorphous powder. Odour none, but very irritating to the nostrils. Taste very bitter and acrid. *Solubility:* 1 in 6 of ether; 1 in 3 of alcohol (90 per cent.); readily in dilute acids; very feebly in water.

Dose, $\frac{1}{64}$—$\frac{1}{16}$ gr. 0·001—0·004 G.

Pure veratrine, $C_{37}H_{51}NO_9$, crystallizes in rhombic prisms, but the veratrine usually seen is very rarely pure.

Action

External Veratrine, if it is applied to the unbroken skin, and especially if it is rubbed in, produces tingling and numbness, followed by a sensation of coldness and anæsthesia to pain, touch, and temperature. Given subcutaneously it causes violent pain and irritation.

Internal. *Gastro-intestinal tract.* Inhalation of the minutest portion causes great irritation of the mucous membrane of the nose, violent sneezing, and a free discharge of mucus, which may be bloody. A speck on the tongue gives rise to burning pain and profuse salivation. In the stomach and intestine it produces great epigastric pain, vomiting, and diarrhœa. These results also occur if it is given subcutaneously.

Circulation. It acts directly on the cardiac muscle as it does upon voluntary muscle: that is to say, the contractions of the heart become fewer, but each lasts a very long while until ultimately the heart stops in systole. It also acts on the vagus as on spinal nerves, the functional activity being first exalted, and this is partly the reason of the slowing of the heart; afterwards the vagus is depressed, but this does not cause a quickening of the pulse, because of the action of the veratrine on the cardiac muscle, but it may make the beat irregular. The blood pressure at first rises from the increased force of the beat, and general vaso-constriction, but as the heart slows it falls. The muscular action is most evident in frogs, the vagal in mammals.

Respiration. Small doses quicken respiration, large ones retard it, producing long pauses, and finally arresting it. These results are probably due at first to stimulation, and afterwards to paralysis of the ends of the vagus in the lung, and to paralysis of the respiratory centres. The temperature is lowered.

Nervous system. The brain is unaffected, and probably veratrine has no influence on the spinal cord. Motor nerves are first excited and then paralysed by large doses, and the same is true of sensory nerves and their endings in smaller doses; but here the primary stimulation is more marked, hence the transient pain produced by local inunction.

Voluntary muscles. The effect of veratrine is peculiar and characteristic. In animals to which it has been given, or in excised muscles to which it is applied, it is found that the period during which a single contraction lasts is enormously prolonged. If a tracing of the contraction be taken it will be seen that the time of the ascent of the curve is unaltered, that the height is greatly increased and the descent is extraordinarily extended. This is a genuine lengthened contraction, which is neither rigor nor tetanus, but it almost exactly resembles the contraction of the muscles met with in Thomsen's disease. This effect of veratrine disappears if the muscle is cooled.

Therapeutics

EXTERNAL Veratrine, like aconite, has been used as an inunction for neuralgia.

PILOCARPINE

Pilocarpinæ Nitras (B.P.). Pilocarpine Nitrate. $C_{11}H_{16}O_2N_2$, HNO_3.

SOURCE. The nitrate of an alkaloid obtained from the leaves of *Pilocarpus microphyllus* and other species of *Pilocarpus.* Jaborandi leaves.

CHARACTERS. A white, crystalline powder. *Solubility:* 1 in 8 of water.

Dose, $\frac{1}{20}$—$\frac{1}{5}$ gr. 3—12 mg.

Action

External. None.

Internal. Pilocarpine is a parasympathomimetic drug with a selective action on the cells innervated by cholinergic fibres. It acts even after nerve degeneration because its effect is in the reactive substance of the cell. Although the results are in many ways similar to those of physostigmine it will be seen that the mode of action is quite different. Furthermore it has none of the nicotine-like action of acetylcholine. Atropine is its antagonist.

Gastro-intestinal tract. Pilocarpine is very quickly absorbed, and soon produces a **great increase in the amount of salivary secretion.** Pilocarpine excites the secretion of the gastric juice, intestinal fluid, and pancreatic secretion. The unstriped muscle of the stomach and intestine and gall bladder is stimulated, and thus the drug may purge. Large doses, especially of jaborandi, may produce vomiting.

Circulation. Pilocarpine has no effect on the blood, but it is a **cardiac depressant.** The pulse rate, it is true, may be, and in the human being always is, a little accelerated at first, but soon it falls. This slowing of the pulse is at once set aside by atropine, but is not prevented by section of the vagus. Vaso-dilatation is usually produced by pilocarpine.

Respiration. In the same way as with other secretions that of the bronchi is greatly increased, and the bronchioles are constricted.

Skin. Pilocarpine produces a very **profuse** secretion of **sweat.** It is the most powerful diaphoretic drug we have. A single dose may cause the flow of fifteen fluid ounces of sweat. It is said that the proportion of urea and chlorides in the sweat is greatly increased. This profuse diaphoresis is explained by the fact that the sympathetic nerves to the sweat-glands are cholinergic. The skin may flush, but this is not the cause of the diaphoresis. Pilocarpine is alleged to encourage the growth of hair.

Kidneys. If the sweating is profuse the secretion of urine is lessened. Pilocarpine is excreted unchanged in the urine.

Temperature. The temperature falls considerably. This is probably due in large part to the evaporation of the perspiration.

Eye. Whether applied locally to the eye or given internally, pilocarpine produces **great contraction of the pupil.** It also causes decreased tension of the eyeball, and an approximation of the nearest and farthest points of distinct vision, due to contraction of the ciliary muscle.

Therapeutics

External. Pilocarpine has been used locally to promote the growth of the hair. The mode of action is not understood. In 2 per cent. solution it has been used in the eye to contract the pupil and reduce intra-ocular pressure.

Internal. Pilocarpine has been used as a diaphoretic in chronic nephritis with **uræmia.** For this purpose $\frac{1}{5}$ of a grain (12 milligrms.) of the nitrate is injected. The sweating is aided by wrapping the patient in several warm blankets, giving him hot drinks, and putting a hot water bottle to his feet. It must be given with great caution when the heart is diseased, for it is a cardiac depressant, and when there is bronchitis, for it increases the bronchial secretion. Injected subcutaneously it has been given as an antidote to belladonna poisoning, but cannot avert death because it antagonizes at the peripheral points of action only.

Muscarine. Muscarine is an alkaloid extracted from a poisonous mushroom, *Agaricus muscarius.*

It acts exactly like pilocarpine except that it produces more nausea and is more toxic. It is not used in medicine.

Choline (**B.P.C.**) is chemically related to muscarine and resembles it pharmacologically in that it slows the heart and increases intestinal movements and the secretions. It exists in many plants, in lecithin, and in the gut contents. **Acetyl-choline** (**B.P.C.**) can be synthetized from choline by the intestinal mucosa and it acts as a natural hormone, stimulating peristalsis. It is 1000 times more powerful than choline and is liberated at the nerve endings when the para-sympathetic is stimulated. Its action is that of para-sympathetic stimulation, causing slowing of the heart and a fall of blood pressure from arteriolar dilatation.

Acetyl-choline hydrochloride. $(CH_3)_3N.Cl.C_2H_4.COO.CH_3$. Has been injected intramuscularly in doses of 0·2 grm. thrice daily for hyperpiesia, Raynaud's disease, threatening gangrene, and paralytic ileus. Its effect on the vascular system, if given intravenously, is quite definite but very transient, for the body destroys it almost instantly. If this were not so, it would follow that activity of any part of the para-sympathetic system would involve the whole.

CARBACHOL

Carbacholum (B.P.). *Tr. Names.* Moryl : Choryl : Doryl. It is carbamylcholine chloride.

Characters. Crystalline, colourless, powder, freely soluble in water.

Dose, $\frac{1}{64}$—$\frac{1}{16}$ gr. 1—4 mg.
$\frac{1}{240}$—$\frac{1}{120}$ gr. 0·25—0·5 mg.—by subcutaneous injection.

Preparation **(B.P.)**

Injectio Carbacholi. Contains 0·25 mg. ($\frac{1}{240}$ gr.) in 1 ml. (15 min.).

Dose, $\frac{1}{240}$—$\frac{1}{120}$ gr. 0·25—0·5 mg.

Action

This drug causes a fall of blood pressure, stimulates the muscle of the digestive tract, bladder, and bronchioles, produces miosis, sweating, lachrymation, salivation, flushing, and gastric juice secretion. Its action is like that of acetylcholine, but being more stable its effects are less evanescent and it can be given by mouth.

Therapeutics

It is of great value in the relief of **urinary retention**, when not due to obstruction. It is also used for **tympanites, paroxysmal tachycardia, Raynaud's disease**, and locally, in 0·5 per cent. solution, for **glaucoma.**

Acetyl-β-methylcholine Chloride (Mecholyl). The action of this drug is similar to that of carbaminoylcholine in that it is a parasympathetic stimulant. It is less stable than the former, but is effective by injection and by mouth. Its special value is that it can be used for local effect as in **Raynaud's disease, varicose ulceration,** and **scleroderma** by administration by ionization. By injection a dose of 10 to 25 mg. appears to be comparable with 0·25 to 0·5 mg. of carbaminoylcholine. Its action on the gastro-intestinal tract is relatively greater than on the cardiovascular system and thus differs from carbaminoylcholine.

Dose, 0·1 to 0·5 per cent. solution for ionization: 20–30 milliamps. for 30 minutes. Direct application to an ulcer is to be avoided.
0·01 to 0·04 G.—by intramuscular injection for paroxysmal tachycardia.
0·0025 G.—by injection for tympanites.
1 G.—by mouth.
0·5 to 1·0 per cent. solution for glaucoma.

PHYSOSTIGMINE and NEOSTIGMINE

Physostigminæ Salicylas (B.P.). $C_{15}H_{21}O_2N_3$, $C_7H_6O_3$. *Synonym.* Eserine salicylate.

SOURCE. The salicylate of an alkaloid obtained from Calabar bean, the seeds of *Physostigma venenosum.*

CHARACTERS. Minute white crystals, becoming red on exposure to light and air. Bitter taste. *Solubility:* 1 in 100.

Dose, $\frac{1}{100}$—$\frac{1}{50}$ gr. 0·6—1·2 mg.

Preparations **(B.P.)**

1. **Lamella Physostigminæ.** Physostigmine salicylate 0·065mg. ($\frac{1}{1000}$ gr.)

2. **Oculentum Physostigminæ.** 0·125 per cent. of physostigmine salicylate.

3. **Injectio Physostigminæ Salicylatis.** Contains 0·6 mg. ($\frac{1}{100}$ gr.) in 1 ml. (15 min.).

Dose, as for Physostigmine Salicylate.

Neostigminæ Bromidum (B.P.). $C_{12}H_{19}O_2N_2Br$. White, crystalline, water-soluble powder.

Dose, $\frac{1}{6}$—$\frac{1}{3}$ gr. 10—20 mg.

Neostigminæ Methylsulphas (B.P.). $C_{13}H_{22}O_6N_2S$.

Dose, $\frac{1}{120}$—$\frac{1}{30}$ gr. 0·5—2 mg.—by subcutaneous or intramuscular injection.

Preparation **(B.P.)**

Injectio Neostigminæ Methylsulphatis. Contains 0·5 mg. ($\frac{1}{120}$ gr.) in 1 ml. (15 min.).

Dose, $\frac{1}{120}$—$\frac{1}{30}$ gr. 0·5—2 mg.

Action

External. None.

Internal. The effects of physostigmine are due to its preventing destruction of acetylcholine by choline esterase at the cholinergic nerve endings. Thus it causes salivation, increased force of gastric and intestinal peristalsis, bradycardia—tachycardia may arise because the drug stimulates the output of adrenaline—rise or fall of blood pressure, small pupils, accommodation for near vision and fall of intraocular pressure (especially when applied locally), and fibrillary twitchings of skeletal muscles. Sweating and bronchiolar constriction also occur. The urinary bladder contracts and the sphincter relaxes.

It is probable that the signs of preliminary excitation and later depression of the central nervous system are due to the partial asphyxia caused by bronchoconstriction.

Therapeutics

Voluntary muscles. Highly beneficial effects are derived from the use of physostigmine, in the treatment of **myasthenia gravis.** One-eighth grain physostigmine salicylate taken in the morning on an empty stomach will abolish symptoms for seven hours or more. Abdominal discomfort and nausea may be prevented by the previous administration of 20 minims of tincture of belladonna. This dose is dangerously high and treatment with the less toxic **neostigmine** (prostigmine) is now performed. The latter drug is a synthetic substance allied pharmacologically to physostigmine: 0·5 mg. by injection or 30 mg. by mouth are given. The injection is used (1) to establish the diagnosis in that symptoms are rapidly relieved; (2) in case of an acute exacerbation of the disease. Otherwise oral administration is employed and the doses so spread as to keep the patient as free as possible from symptoms. In some two doses a day suffice, in others the drug must be taken four times daily.

Involuntary muscles. Because it stimulates nerve terminals in unstriped muscles physostigmine has been recommended for chronic constipation, atony of the bladder, and chronic bronchitis with deficient power of expectoration. Prostigmine is extensively used for post-operative **intestinal atony.**

Eye. The lamellæ and oculentum are used in the eye to diminish intra-ocular tension, in **glaucoma,** to **contract the pupils** of patients under treatment with belladonna alkaloids for Parkinsonism, and to prevent prolapse of the iris after wounds or ulcers of the cornea. If used in solution, $\frac{1}{2}$ to 2 gr. (0·03 to 0·12 grm.) of physostigmine salicylate to 1 fl. oz. (30 mils) of water is the usual strength.

Antagonisms

It will be observed that in its actions on the pupil, on secretion, on the heart, and on respiration, physostigmine is antagonistic to atropine. The mutual antagonism of curarine and physostigmine on voluntary muscle is very striking.

GROUP XVI

Nitrites

AMYL NITRITE

Amylis Nitris (B.P.). It contains not less than 90 per cent. w/w of nitrites calculated as $C_5H_{11}O_2N$.

CHARACTERS. An ethereal liquid of a pale yellow colour, and smelling strongly like pear drops, which are flavoured with amyl acetate. Very volatile. Soluble in ether, chloroform, or spirit, but not in water.

Dose, 2—5 min. 0·12—0·3 ml.—by inhalation.

Action

External. None.

Internal. The following account will refer to the effects of inhalation. The effects of a single inhalation pass off in two or three minutes. Absorption takes place through the alveoli of the lungs.

Circulation. Within a minute of inhalation the **face flushes**, the **heart** beats very **rapidly** and **violently**, there is a throbbing in the head, and the vessels, *e.g.* the carotids, may be seen to pulsate actively. Headache, giddiness, dilatation of the pupils, and increased respiratory movements quickly supervene. The vessels of the body rapidly dilate, but of the cutaneous vessels those of the head and neck are chiefly affected. This is due to a direct action on the arterioles, for it happens if the cord is destroyed. It is the unstriped muscles of the arterioles, and not the ends of the nerves, which are affected. The blood pressure and arterial tension of course fall very low. The increase in the rate of the pulse is unaccompanied by any alteration in the force of the beat; it is apparently due to a depressing influence on the inhibitory vagus centre as a result of lowered blood pressure. The coronary arteries dilate with the other arteries of the body, but in experimental animals the blood supply to the heart is reduced: it is unlikely that the latter effect ever occurs in man with therapeutic doses. In toxic doses the heart may be arrested in diastole from direct action on the cardiac muscle.

Respiration. The rapidity and depth of respiration are at first increased, from stimulation of the respiratory centre by the low blood pressure; this is later depressed, the breathing becoming slower and shallower and death occurs from asphyxia. Nitrites relax the bronchial muscles.

Nervous system. Many of the symptoms referable to the nervous system are secondary effects of the dilatation of the vessels of the brain and spinal cord. Such are the throbbing, sense of fullness, giddiness, and headache noticed directly after inhalation. The headache may remain some time. If much has been inhaled there is unsteadiness of gait and general restlessness. The pupil dilates, and disturbances of vision are present. The function of sensory nerves, motor nerves, and muscles is depressed by the local application of the drug to them, but not after inhalation until shortly before death.

Temperature. Amyl nitrite causes this to fall both in fever and health. The fall is due to the peripheral vascular dilatation, and, if large doses are given, to the changes in the blood.

Urine. The drug escapes in the urine as nitrites and nitrates; it is slightly diuretic, and may cause glycosuria if injected subcutaneously.

Blood. Nitrites given in medicinal doses circulate partly as sodium nitrite, but much is oxidized to nitrate. Outside the body they greatly diminish oxidation, and the same takes place in the blood. After the inhalation of a considerable amount (more than is usually given to a man) the arterial and venous blood both become a uniform chocolate colour. This is due to the formation of methæmoglobin and another body, probably nitric oxide hæmoglobin. The hæmoglobin can no longer absorb oxygen, and hence its oxidizing power is abolished.

Therapeutics

The inhalation of amyl nitrite usually abolishes the pain of **angina pectoris** within a few minutes. The pain of angina is probably due to irritation of sensory nerve-endings in the heart by unoxidized products of muscular contraction. Failure of oxidation is referable to constriction of the coronary vessels or their mouths: they are thus unable to supply sufficient blood to the myocardium to allow it to cope with the increased demand of muscular effort. Nitrites dilate the coronary arteries and thus allow more blood to reach the myocardium. When inhaled amyl nitrite reaches the coronary arteries several seconds before the whole of the systemic system. It thus induces their dilatation before there is a general lowering of blood pressure and will, therefore, powerfully augment the blood-flow through the coronary system for the duration of several heart beats. **Achalasia** of the œsophagus is temporarily relieved by the inhalation of amyl nitrite.

In certain spasmodic states such as occur in **biliary, renal** and **intestinal colic** and in **asthma**, nitrites may be of great benefit in inducing relaxation of plain muscle. For the same reason the fumes of smouldering saltpetre (asthma papers) are inhaled to obtain the action of the nitrite produced by reduction.

Octyl Nitrite (2 ethyl-n-hexyl-l-nitrite) is another volatile nitrite having a more prolonged action than amyl nitrite. Its action is less violent and the unpleasant throbbing of the head is seldom produced by it. It may be used for the same purposes as amyl nitrite. It is claimed that it is very effective in achalasia of the œsophagus.

ETHYL NITRITE

Spiritus Ætheris Nitrosi (B.P.). *Synonym.* Sweet spirit of nitre. It contains 4 per cent. of ethyl nitrite.

Characters. Transparent, nearly colourless, inflammable, slightly acid liquid of an apple-like odour and a sweet, cooling taste. *Strength:* It must contain between 1·25 and 2·5 per cent. w/v of ethyl nitrite.

Dose, 15—60 min. 1—4 ml.

Action

External. Spirit of nitrous ether evaporates when it is applied externally, and a slightly anæsthetic effect is produced.

Internal. It combines the action of the ether with that of the nitrites contained in it. If prescribed in water the nitrite escapes and the action is largely that of ether and alcohol. Because of the ether it is a **carminative.** Because of the nitrites it acts like amyl nitrite; but as the ethyl nitrite is so diluted, its action in this direction is feeble: thus it only **moderately dilates the vessels,** leading to a **diaphoretic** effect on the skin, a **diuretic** effect on the kidneys, and a lowering of arterial blood pressure. The dilatation of the cutaneous vessels and the sweating produce a slight antipyretic influence.

Therapeutics

For its diaphoretic and slight antipyretic effects it is commonly given in mild febrile attacks, such as a common cold. It is also used as a diuretic.

NITROGLYCERIN

Trinitroglycerin. $C_3H_5[(NO_2)O]_3$.

Synonyms. Trinitrin, Glonoin oil, Nobel's blasting oil.

SOURCE. Glycerin is dropped into a mixture of sulphuric and nitric acids kept cool by ice.

CHARACTERS. A colourless oily liquid, slightly soluble in water, easily in fats, oil, alcohol, ether. Highly explosive. Mixed with silica forms dynamite.

Preparation (B.P.)

Tabella Glycerylis Trinitratis. Nitroglycerin; chocolate. Each contains $\frac{1}{130}$ gr.—0·5 mg. of nitroglycerin.

Dose, 1 or 2 tablets.

Action and Therapeutics

Its action is the **same as** that of **amyl nitrite,** but is more powerful because it is not broken up in the stomach as are the metallic nitrites. On reaching the blood it breaks up into glycerine, nitrates and nitrites. Some of the drug circulates unaltered, and this is probably responsible for the headache which it induces. The effects of nitroglycerin are **more persistent,** and if administered by the mouth, they are slower in their onset. It is given for **angina pectoris.** It has been shown that if the tablets be allowed to dissolve under the tongue absorption and action are much more rapid than when the drug is swallowed. In fact, if administered sublingually, nitroglycerin is efficient in an attack and of superlative value in preventing recurrence. For this purpose one or two tablets should be sucked, or allowed to dissolve under the tongue, before unavoidable physical effort or emotional stress, *e.g.* speech-making. If more than four or five are taken in the day, headache is apt to be troublesome. The presence of chocolate in the tablet encourages its retention in the mouth. The point of this is that it enables the drug to be absorbed into the systemic circulation and thus to avoid preliminary passage through the liver.

SODIUM NITRITE

Sodii Nitris (B.P.). $NaNO_2$.

CHARACTERS. A white crystalline deliquescent powder, very soluble in water.

Dose, ½—2 gr. 30—120 mg.

Action and Therapeutics

The action of sodium nitrite is the **same as** that of **amyl nitrite** and other nitrites. It is administered by mouth and partly decomposed in the stomach with liberation of nitrous acid. This causes eructation and gastric irritation. It is suitable for the same cases as nitroglycerin, being **slower and gentler** in action than amyl nitrite. Sodium nitrite has the same action on the blood as amyl nitrite.

GROUP XVII

Antipyretics

Antipyretics, or Drugs which decrease the Bodily Temperature. There are few drugs which can markedly lower the temperature in health. Some, it is true, will cause the temperature to fall below normal if given to a healthy man in large enough doses to induce severe collapse. The word antipyretic is limited to those drugs which bring down the temperature when it is raised owing to disease. We know that the greatest amount of heat is produced in the muscles and a considerable amount in the glands, a centre in the hypothalamus controlling heat balance ; that heat is lost mostly by radiation from the vessels of the skin and by the evaporation of sweat, and that these vessels and the sudoriparous glands are under that lost through the lungs and excreta. The production and loss are in health accurately adjusted by virtue of a hypothalamic centre whose function it is to maintain the balance between the production and the loss. Also all parts of this complex mechanism are supplied with blood vessels, and must be affected by the quantity and composition of the blood supplied to them.

In fever the heat-regulating centre is set like a thermostat at a higher level than normally. Antipyretics act by lowering this level. The body then responds by a great increase in heat loss and slight reduction of heat formation.

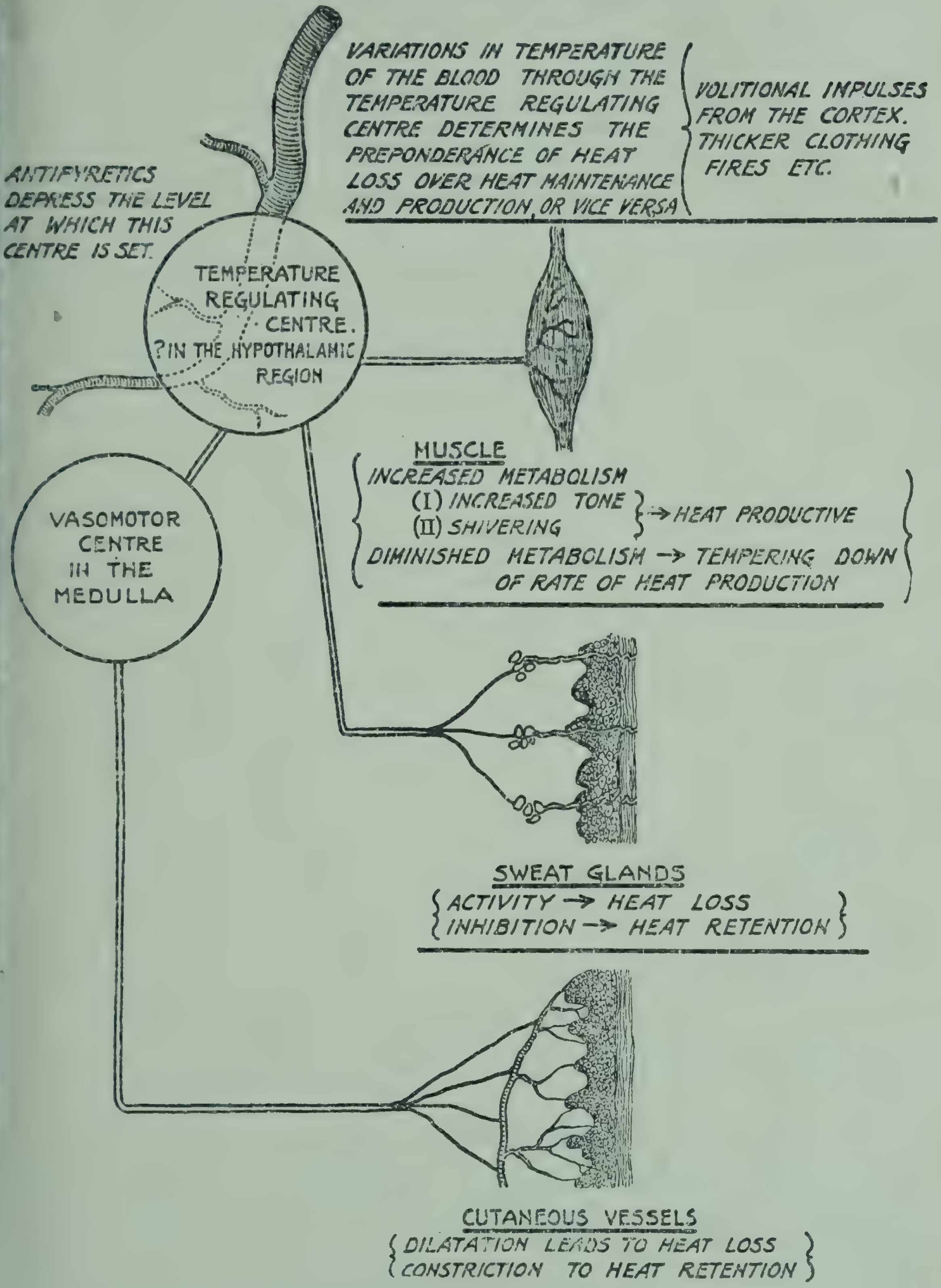
Action of antipyretics. All sudorifics and all dilators of the cutaneous vessels act as antipyretics. Cold, such as a cold bath, increases the loss of heat by direct abstraction.

The action of antipyretics such as **phenacetinum, phenazonum** (antipyrin), and **acetanilidum** (antifebrin), **salicylic acid, acetyl salicylic acid** (aspirin) and **salicin** is to reduce the temperature in fever by their effect on the central heat-regulating mechanism. This in its turn produces marked cutaneous vaso-dilatation and sweating, with consequent increase of heat loss. Heat production is also decreased.

Therapeutics. The use of antipyretics is very limited because **the reduction of temperature is rarely indicated.** The group is used chiefly for its analgesic action referred to below.

Cold is more often employed, either by cold sponging,

Temperature Regulating Mechanism


VARIATIONS IN TEMPERATURE OF THE BLOOD THROUGH THE TEMPERATURE REGULATING CENTRE DETERMINES THE PREPONDERANCE OF HEAT LOSS OVER HEAT MAINTENANCE AND PRODUCTION, OR VICE VERSA
VOLITIONAL INPULSES FROM THE CORTEX. THICKER CLOTHING FIRES ETC.
ANTIPYRETICS DEPRESS THE LEVEL AT WHICH THIS CENTRE IS SET.
TEMPERATURE REGULATING CENTRE. ?IN THE HYPOTHALAMIC REGION
VASOMOTOR CENTRE IN THE MEDULLA
MUSCLE
INCREASED METABOLISM
(I) INCREASED TONE
(II) SHIVERING
→ HEAT PRODUCTIVE
DIMINISHED METABOLISM → TEMPERING DOWN OF RATE OF HEAT PRODUCTION
SWEAT GLANDS
ACTIVITY → HEAT LOSS
INHIBITION → HEAT RETENTION
CUTANEOUS VESSELS
DILATATION LEADS TO HEAT LOSS
CONSTRICTION TO HEAT RETENTION

ice, or a cold bath. Sponging with hot water will, by the vascular dilatation and subsequent sweating it induces, reduce a febrile temperature.

Of the drugs which alter the production, acetanilide and phenazonum are dangerous because of the collapse they may produce; quinine and salicylic acid are rather uncertain, except in malaria and rheumatic fever respectively. Phenazonum and phenacetinum and aspirin are most in demand. They are certain antipyretics. Phenacetin is very safe, but less powerful. They are quickly absorbed, and so act promptly.

ACETANILIDE

Acetanilidum (B.P.C.). C_8H_9NO. *Synonyms.* Antifebrin, Phenyl-acetamide.

Source. Glacial acetic acid and aniline are heated together. Acetanilide is distilled over and purified.

Characters. Colourless scaly crystals of a pungent taste. *Solubility:* 1 in 200 of cold water, 1 in 18 of boiling; 1 in 4 of alcohol (90 per cent.); freely in ether and chloroform.

Dose, 2—5 gr. 0·12—0·3 G.—in cachets or suspended.

PHENAZONE

Phenazonum (B.P.). $C_{11}H_{12}N_2O$. *Synonym.* Antipyrin. It is phenyl-dimethyl-isopyrazolon.

Characters. Colourless, odourless, scaly bitter crystals, freely soluble in water.

Dose, 5—10 gr. 0·3—0·6 G.

Preparation (B.P.)

Tabellæ Phenazoni. Contain 5 gr.—0·3 G. in each.

PHENACETIN

Phenacetinum (B.P.). $C_{10}H_{13}NO_2$. *Synonym.* Acetphenetidin.

Source. Glacial acetic acid is made to act upon paraphenetidin.

Characters. Colourless, tasteless, scaly crystals, very sparingly (1 in 1700) soluble in water. Soluble in 20 parts of alcohol (90 per cent.).

Dose, 5—10 gr. 0·3—0·6 G.

Preparation (B.P.)

Tabellæ Phenacetini. Contain 5 gr.—0·3 G. in each.

AMIDOPYRINE

Amidopyrina (B.P.). $C_{13}H_{17}ON_3$. *Unoff. Synonym.* Pyramidon.

It is dimethyl-amino antipyrine.

CHARACTERS. Colourless crystals; almost tasteless. *Solubility:* 1 in 18.

Dose, 5—10 gr. 0·3—0·6 G.

Actions of Acetanilide, Phenazone, Phenacetin, and Amidopyrine

With the exception of phenazone and amidopyrine, the common antipyretics owe their action to para-amidophenol derivatives which are formed in the body. The quicker their formation, the more toxic the drug because of the formation of methæmoglobin.

Blood. With ordinary doses of these drugs this fluid is unaffected, but in large doses the colour is changed from the formation of methæmoglobin. The passage of this in the urine discolours it. Acetanilide causes the red corpuscles to break up, and arrests the movements of the white.

Heart. All four, in large doses, **depress the heart,** probably owing to a paralysing action on the cardiac muscle. This cardiac depression is much less marked with phenacetin and amidopyrine than the other two, and is perhaps less with phenazone than acetanilide. Some persons, especially weakly women, are particularly susceptible, and the dangerous symptoms described under Toxicology may be easily produced.

Respiration This is not affected by ordinary doses. After toxic doses the force of the respiratory act progressively diminishes.

Kidneys. Large doses of any of these drugs cause the urine to be dark owing to methæmoglobinuria. Phenazone and amidopyrine are quickly excreted as such combined with sulphuric acid. The other two often lead to the appearance of glycuronic acid in the urine.

Skin. Any of these four drugs may produce an erythematous rash which is usually morbilliform or urticarial, and they are occasionally mild diaphoretics.

Temperature. These four substances are all **antipyretics** and act chiefly on the central thermotaxic mechanism, so that the temperature of the fevered patient is adjusted for a lower level.

Nervous system. These drugs are powerful **analgesics**, their point of action being in the mid-brain. Acetanilide and phenazone in large doses are said to produce first convulsions, then coma. The effect is attributable to the changes in the blood and cerebral depression.

Therapeutics

Internal. *Pyrexia.* Originally these drugs were introduced into medicine on account of the property they have of reducing pyrexia. The opinion now is, however, that if the temperature is not dangerously high no attempt should be made to reduce it, for the raised temperature is an endeavour on the part of the body to defend itself against the micro-organisms which are the cause of the particular fever from which the patient is suffering ; in other words, the pyrexia is a " defensive mechanism." Further, these drugs are all cardiac depressants, and therefore unsuitable for patients suffering from fever, and this last consideration makes many physicians prefer to use tepid sponging rather than drugs when the temperature is so high that it is considered that it, in itself, is dangerous. Should it, however, for any reason be decided to give one of these drugs as an antipyretic, amidopyrine and phenacetin have the great advantage of depressing the heart very little, and rarely producing the alarming toxic effects described below. They are slower and less powerful in action than the other two, but the effect lasts longer. The danger of **agranulocytosis** is rapidly eliminating amidopyrine from therapeutics, however. The most frequently employed antipyretic and analgesic is acetyl-salicylic acid.

Analgesic action. All these drugs have the property of relieving pain. It is least marked with acetanilide, most with phenazone ; phenacetin and aspirin are to be preferred. They are largely used to relieve the pains of neuralgia, sciatica, dysmenorrhœa, migraine and various headaches.

Toxicology

All these drugs occasionally produce in man collapse, cyanosis, very slow respiration, a feeble and irregular pulse, vomiting, profuse sweating, and profound prostration. Many deaths have been caused by them. It has been stated that during one epidemic of influenza in Vienna seventeen persons were killed by phenazone. Acetanilide is most likely, and phenacetin least likely, to be accompanied by symptoms of poisoning. Any of these drugs may produce a rash, most often like measles or scarlet fever, but sometimes like pemphigus.

Treatment. Wash out the stomach. Strychnine or caffeine subcutaneously to stimulate the medulla. Oxygen inhalations. Warmth to the feet and body. Blood transfusion.

Idiosyncrasy

Certain individuals, particularly women, exhibit a marked idiosyncrasy to amidopyrine. The chief and most dangerous evidence of this is a profound fall in the number of granular leucocytes due to a toxic effect on these in the circulation and on the bone marrow. This condition of agranulocytosis may arise after the use of quite small doses over a short period, *e.g.* a total of 15 grs., and usually proves fatal.

Simple and thrombocytopœnic purpura are other manifestations of idiosyncrasy.

GROUP XVIII

Cinchona Bark, Quinine, Quinidine, Pamaquine, Mepacrine

CINCHONA BARK

Composition. The chief constituents of cinchona bark are four alkaloids, two acids, a glucoside, tannin, a colouring matter, and a volatile oil. (There are twenty cinchona alkaloids, but only four are important.)

1. *Quinine.* $C_{20}H_{24}N_2O_2$. White acicular crystals, very bitter. Lævo-rotatory. Soluble in ether and in ammonia.

2. *Quinidine.* $C_{20}H_{24}N_2O_2$. Isomeric with quinine. Dextro-rotatory.

3. *Cinchonine.* $C_{19}H_{22}N_2O$. Dextro-rotatory.

4. *Cinchonidine.* $C_{19}H_{22}N_2O$. Isomeric with cinchonine. Lævo-rotatory.

Totaquina (B.P.). Totaquine.

Source. A mixture of alkaloids from the bark of *Cinchona succirubra* and other species of Cinchona. Contains not less than 70 per cent. of crystallizable cinchona alkaloids, of which not less than $\frac{1}{5}$ is quinine.

Characters. Pale grey or brown powder; taste bitter. Insoluble in water; soluble in warm alcohol.

Dose, 5—10 gr. 0·3—0·6 G.

Quininæ Sulphas (B.P.). Quinine Sulphate. $([C_{20}H_{24}N_2O_2], H_2SO_4)_2, 7\frac{1}{2}H_2O$.

CHARACTERS. Filiform, silky, very light, snow-white crystals, with an intensely bitter taste. *Solubility:* 1 in 800 of water; easily in slightly acidulated water (1 ♏ of a mineral acid in 2 fl. oz. of water will dissolve 1 gr. of sulphate of quinine). Solution is lævo-rotatory.

Dose, 5—10 gr. 0·3—0·6 G.

Quininæ Bisulphas (B.P.). Quinine acid sulphate. $C_{20}H_{24}O_2N_2, H_2SO_4, 7H_2O$.

CHARACTERS. Colourless crystals; bitter taste. *Solubility:* 1 in 10.

Dose, 5—10 gr. 0·3—0·6 G.

Preparation **(B.P.)**

Tabellæ Quininæ Bisulphatis. Contain 5 gr.—0·3 G. in each.

Quininæ Hydrochloridum (B.P.). Quinine Hydrochloride. $C_{20}H_{24}N_2O_2HCl, 2H_2O$.

SOURCE. The hydrochloride is obtained from quinine.

CHARACTERS. Crystals resembling those of the sulphate, but larger. *Solubility:* 1 in 32 of water, 1 in 2 of alcohol (90 per cent.).

Dose, 5—10 gr. 0·3—0·6 G.

Preparations **(B.P.)**

1. **Injectio Quininæ et Urethani.** Contains 12·5 per cent. quinine hydrochloride, 6·25 per cent. urethrane, chlorocresol, and distilled water.

   Dose, 8—75 min. 0·5—5 ml.—by intravenous injection, as a sclerosing agent.

2. **Tabellæ Quininæ Hydrochloridi.** Contain 5 gr.—0·3 G. in each.

Quininæ Dihydrochloridum (B.P.). Acid Quinine Hydrochloride. $C_{20}H_{23}O_2N_2, CO_2, C_2H_5$.

CHARACTERS. The acid hydrochloride is a white crystalline powder, soluble in less than its own weight of water and yielding an acid liquid.

Dose, 5—10 gr. 0·3—0·6 G.—by mouth or by intravenous injection.

Preparation **(B.P.)**

Injectio Quininæ Dihydrochloridi. Contains 0·3 G. (5 gr.) in 5 ml. (75 min.). Must be diluted with 10 times its volume of Injection of Sodium Chloride and injected slowly intravenously.

Quininæ et Æthylis Carbonas (B.P.). Quinine Ethyl Carbonate. $C_{20}H_{23}N_4O_4, 2HCl$.

CHARACTERS. Fine needles, *almost tasteless.* Slightly soluble in water; readily in alcohol.

Dose, 5—10 gr. 0·3—0·6 G.

Quinidinæ Sulphas (B.P.). Quinidine Sulphate.

CHARACTERS. Colourless, bitter crystals. *Solubility:* 1 in 90 of water; 1 in 10 of alcohol (90 per cent.).

Dose, 1—5 gr. 60—300 mg.

Actions of Cinchona Bark and its Alkaloids

The action of cinchona bark is due almost entirely to the alkaloids in it.

External. Quinine is **antiseptic** by virtue of its property of being a protoplasmic poison. In other words it does not possess the specific affinity for certain tissues with disregard for others such as is exhibited by the majority of alkaloids. Solutions of 1 : 1000 inhibit the growth of, or destroy, most pathogenic bacteria, and alcoholic and lactic fermentation are arrested. Spermatozoa are paralysed by weak concentrations, and the amœboid movement of leucocytes, and inflammatory diapedesis, are arrested by the local application of the alkaloid in a concentration of 1 : 3000. This strength is never attained by therapeutic doses, however, but much weaker concentrations interfere with phagocytosis. Enzyme action is stimulated by very dilute solutions and destroyed by higher concentration. This is, in fact, the general effect on all protoplasm.

Internal. *Alimentary canal.* Quinine acts like any other bitter. Its salts irritate the mucosa and may produce vomiting or diarrhœa. Quinine and ethyl carbonate and quinine tannate are only slightly bitter. The latter disintegrates very slowly in the intestine and much may fail to be absorbed. Quinine is absorbed from the intestine.

Circulation. Quinine acts like quinidine on heart muscle, reducing conductivity and excitability and lengthening the refractory period. In these effects it is weaker than quinidine. Large doses (larger than are given to man medicinally), either applied to the excised heart or circulating through it, directly paralyse the organ. Large doses lower the blood pressure considerably; this is owing partly to the effect on the heart, but chiefly on the walls of the peripheral vessels which are dilated.

Respiration. Small doses slightly increase, large doses depress, the respiration owing to action on the respiratory centre. Death is due to this.

Temperature. It is a powerful **antipyretic** in malaria, because it destroys the parasites, in other diseases its antipyretic effect is less. In large doses it causes a slight fall of a healthy temperature by directly diminishing heat production in the muscles.

Central nervous system. There is initial slight stimulation of the cord followed by depression. The latter effect only is exerted on the brain, and is responsible for a mild analgesic and antipyretic action.

Uterus. Quinine acting on the uterine musculature causes it to contract rhythmically. If taken in a single large dose, or if injected in moderate amount intravenously, or if taken in small doses for a long time it often produces uterine bleeding, even in an intermenstrual period, and frequently gives rise to menorrhagia. Abortion may follow its use. Labour can often be induced by it at full term.

Skeletal Muscle. The cinchona alkaloids lengthen the refractory period and decrease the excitability of the motor end-plate. They inhibit responses to a tetanizing stimulus, to acetylcholine, physostigmine, and veratrine. They potentiate the action of curare. Quinine aggravates myasthenia gravis and relieves the symptoms of myotonia congenita.

Kidneys. After a full dose of quinine it is found in the urine in half an hour, and is slowly excreted for several days, but by far the greater part of that excreted is eliminated within the first forty-eight hours. More than half of the alkaloid is, however, completely destroyed in the body. It is not stored in any organ, though traces may be found in all the secretions. It appears to circulate in the blood in a condition of adsorption to the corpuscles.

Metabolism. This is unaffected by quinine.

Cinchonism. In many persons quinine produces ringing in the ears, fullness in the head, and slight deafness. With larger doses these symptoms increase, disturbances of vision and giddiness are added. The patient may stagger when he walks, and the headache may be very intense.

Delirium, coma, deafness, and blindness may precede death from cardiac and respiratory failure. Great congestion of the middle ear and labyrinth is found in animals poisoned by quinine. The mild degrees of cinchonism pass off directly the drug is discontinued. People with idiosyncrasies in regard to quinine may develop, from small doses, epileptiform fits, unconsciousness, cyanosis, and enfeebled heart's action. In the susceptible, quinine causes an erythematous rash, and it may give rise to epistaxis and other hæmorrhages. Those who work among cinchona barks may have a rash on their skin from the mechanical irritation of the powder.

Quinidine is very similar to quinine. It is excreted more quickly. **Its effect in reducing the conductivity and excitability of the heart muscle and in lengthening the refractory period is at least five times as great.**

Cinchonine and especially Cinchonidine resemble quinine, but are also convulsants.

Therapeutics

Internal. *Gastro-intestinal Tract.* It is used as a simple bitter in the form of the compound tincture.

Heart. Quinidine, by prolonging the refractory period of the myocardium, may abolish **auricular fibrillation.** Five gr. of the sulphate are given in a cachet once on the first day, twice on the second, and so on up to eight doses per diem. As a rule the fibrillation, if amenable to this treatment, ceases on the third or fourth day. Failure to obtain this result is attributable to the depression of conductivity of the heart muscle. The circus-movement may thus continue in spite of the increase of the refractory period. Quinidine is of chief value when fibrillation is unassociated with gross structural changes in the heart.

Specific Action. Quinine, and other cinchona alkaloids, arrest the paroxysms of **malaria.** If 30 to 45 gr. (2 to 3 grms.) of quinine be taken about three hours before the attack is due, it will either not take place, or it will be very mild, for the quinine in the blood will kill the spores when they are set free from the malarial parasite. The same effect follows if smaller doses, about 10 gr. (0·6 grm.), are taken four or five times a day between the attacks. Not only is it thus prophylactic, but the continued use of it is curative, giving 10 gr. a day for three months. The dihydrochloride is sometimes used intravenously for cerebral malaria and must be given slowly. Quinidine is equally effective for malaria but too depressant for the heart. Totaquina has been introduced for the treatment of malaria because it is much cheaper than the pure alkaloids.

Myopathies. Quinine is of great value in the treatment of **myotonia congenita** and to some extent in **myotonia atrophica.** A dose of 10 gr. t.d.s. suffices. It may be tried also for dystonia musculorum deformans and spasmodic torticollis. A test dose will reveal suspected myasthenia gravis.

Varicose Veins. The official injection of quinine and urethane is used for the injection treatment of varicose veins. The alkaloid irritates the endothelium, thereby inducing thrombosis.

Contraception. Quinine hydrochloride pessaries (gr. iij in cocoa butter) are used very extensively as contraceptives. Solutions are used for vaginal douching with the same object. It is of interest to note that the spermicidal effect of the alkaloid is greatly reduced by the presence of the greasy basis of the pessary. It is thought that the mechanical barrier of the cocoa butter is probably the more effective agent.

Quinine should if possible be avoided in (1) persons suffering from acute or subacute disease of the middle ear ; (2) those suffering from gastro-intestinal irritation, which it may increase ; (3) those people, occasionally met with, in whom quite small doses produce very severe symptoms of cinchonism.

If it is wished to give quinine intravenously, intramuscularly or hypodermically, the best salts are the lactate (soluble 1 in 5 of water) or the official acid hydrochloride. The relatively tasteless salts are suitable for children.

Pamaquinum (B.P.). $C_{42}H_{45}O_7N_3$. *Tr. Names.* Plasmochin, Plasmoquine, Beprochin.

CHARACTERS. Yellow, bitter powder, insoluble in water.

Dose, $\frac{1}{6}$—$\frac{1}{3}$ gr. 10—20 mg.

This drug, which is a quinoline derivative, is used for **malaria.** It is most effective in benign tertian and quartan malaria, but less efficient than quinine in the treatment of subtertian (malignant) infection in that although it is particularly valuable here in destroying the sexual forms (gametocytes) it is inactive to the asexual schizonts. The reverse applies to quinine. A combination of the two is thus ideal. Of particular importance is the fact that the drug renders crescents non-infective to anopheline mosquitoes for three days after a single dose. Tertian and quartan malaria can usually be eradicated by the combination of 0·01 grm. pamaquin and 0·125 grm. quinine thrice daily for a week; the course to be repeated four times with four-day intervals. Too large doses lead to cyanosis and methæmoglobinuria.

Warburg's tincture is a medicine which has a very high reputation in India for malaria. It has been called Tinctura Antiperiodica. The published formula states that it is a tincture made with alcohol (57 per cent.), and containing quinine sulphate, 1 in 50; Socotrine aloes, 1 in 40; opium, 1 in 4000; rhubarb, 1 in 125; camphor, 1 in 500; with angelica seed, elecampane, saffron, fennel, gentian, zedoary, cubebs, myrrh, and white agaric as aromatics. Dose, 1 to 4 fl. dr. (4 to 16 mils). It is often prescribed to be made without the aloes.

Mepacrinæ Hydrochloridum (B.P.) *Synonym.* Quinacrine Hydrochloride. *Tr. Name.* Atebrin..

CHARACTERS. A yellow powder with bitter taste. *Solubility:* 1 in 30, with the formation of a bright yellow, fluorescent, solution.

Dose, 1½ gr.—0·1 G.—prophylactic daily.
3—8 gr. 0·2—0·5 G.—therapeutic daily in divided doses.

Preparation (**B.P.**)

Tabellæ Mepacrinæ Hydrochloridi. Contain 1½ gr.—0·1 G. in each.

Action and Therapeutics

This synthetic dye, a derivative of acridine, was introduced in 1930 for the treatment of malaria. It has a selective action on the schizonts and gametocytes of tertian and quartan malaria. The ring forms thus disappear after two days' treatment, and the temperature falls almost instantaneously. The gametocytes gradually disappear. Treatment is most efficacious if combined with quinine 10 grs. daily. The drug is well tolerated but occasionally causes abdominal pain and yellowness of the skin.

Mepacrine and pamaquin must not be given concurrently because this increases the toxic effects of each. Mepacrine may be given with quinine in doses of 0·1 grm. three times a day for a week and then followed by pamaquin 0·01 gm. thrice daily for six days.

Mepacrinæ Methanosulphonas (B.P.).

Dose, 1½—5 gr. 0·1—0·3 G.—by intramuscular injection.

Preparation (B.P.)

Injectio Mepacrinæ Methanosulphonatis.

Dose, 1½—5 gr. 0·1—0·3 G.—freshly prepared solution given intramuscularly.

Action and Uses

The action is similar to that of the hydrochloride. The drug is used for injection of severe cases of malaria.

Paludrine. This is a synthetic drug belonging to an entirely new chemical series of anti-malarials. It is a pyrimidine derivative in which is included a guanidine group. It is the first drug to have the property of depressing or destroying the exo-erythrocytic phase of avian malaria (*P. gallinaceum*). It destroys the same phase of *P. falciparum* fully protecting volunteers against viable sporozoites. It merely inhibits *P. vivax* infections (induced).

It has a low toxicity. In large doses it causes abdominal pain and vomiting. The optimum dosage has yet to be determined. It appears to be about **0·3 grm.** daily for 14 days.

Quinine and Urea Hydrochloride (B.P.C.). $C_{20}H_{24}O_2N_2$, HCl $CO(NH_2)_2$, HCl. $5H_2O$. Injected subcutaneously or applied to mucous membranes, it acts as a powerful anæsthetic, and the effects may last a week. It paralyses sensory nerve endings. Solutions of 0·5 to 1 per cent. have been used for rectal operations. In Crile's anoci-association method of anæsthesia large quantities of 0·25 to 0·5 per cent. solution are injected to produce complete nerve block and prevent post-operative shock and pain. For painful sore throat 20 per cent. solutions may be applied locally. Suppositories (containing 5 grains) and ointments (20 per cent.) are used for piles and rectal pain.

Dose, ½—15 gr. 0·03—1 G. by injection.

GROUP XIX

Salicin, Salicylates, Benzoin, Benzoates

SALICIN

Salicinum (B.P.C.). $C_{13}H_{18}O_7$. A crystalline glucoside obtained from the bark of various species of *Salix* and of *Populus*.

Acidum Salicylicum (B.P.). $C_7H_6O_3$. Orthohydroxybenzoic acid.

SOURCE. Made by the interaction of sodium phenate and carbon dioxide.

CHARACTERS. Colourless crystals. Inodorous. Taste first sweetish, then acid. *Solubility:* 1 in 500 of water. Readily in alcohol, ether, and hot water.

Preparation **(B.P.)**

Unguentum Acidi Salicylici. Salicylic acid, 2 per cent.

Sodii Salicylas (B.P.). Sodium Salicylate. $NaC_7H_5O_3$.

SOURCE. Obtained by acting on sodium carbonate with salicylic acid.

CHARACTERS. Colourless crystals. Odour none. Taste sweetish saline. *Solubility:* 1 in 1 of water (but when this solution stands the salt containing 6 molecules of water of crystallization may be deposited), 1 in 6 of alcohol (90 per cent.).

Dose, 10—30 gr. 0·6—2 G.

Preparation **(B.P.)**

Tabellæ Sodii Salicylatis. Contain 5 gr.—0·3 G. in each.

Methylis Salicylas (B.P.). It contains not less than 98 per cent. of pure methyl salicylate, $C_8H_8O_3$.

SOURCE. Obtained by the interaction of methyl alcohol and salicylic acid. (It is the chief constituent of oil of wintergreen.)

CHARACTERS. A colourless liquid, aromatic odour, warm sweetish taste, almost insoluble in water, readily in alcohol.

It is an ingredient of Cataplasma Kaolini.

Acidum Acetylsalicylicum (B.P.). Acetylsalicylic Acid, $C_9H_8O_4$.

Synonym. Aspirin.

SOURCE. May be obtained by the action of acetic anhydride or of acetyl chloride on salicylic acid.

CHARACTERS. A white, crystalline powder; taste slightly acid. Sparingly soluble in water.

Dose, 5—15 gr. 0·3—1 G.

Preparations (B.P.)

1. **Tabellæ Acidi Acetylsalicylici.** Contain 5 gr.—0·3 G. in each.

2. **Tabellæ Acidi Acetylsalicylici cum Ipecacuanha et Opio.** Contain 2½ gr. (0·16 G.) aspirin, and 2½ gr. of Dover's Powder.

3. **Tabellæ Acidi Acetylsalicylici et Phenacetini.** Contain 3½ gr. (0·23 G.) aspirin and 2½ gr. (0·16 G.) phenacetin.

Action of Salicin and Salicylates

External. Salicin and salicylic acid are **antiseptics.** They are stimulant and mildly irritant to the skin. Locally applied they **check sweating.** Sodium salicylate is less antiseptic. Salicylic acid softens and removes epithelium. Methyl salicylate is rapidly absorbed when rubbed into the skin.

Internal. *Alimentary Tract.* When inhaled or applied to the throat, salicylic acid is irritating, causing sneezing and coughing. In the stomach also it is irritant, giving rise to pain, nausea, and vomiting unless well diluted, and should therefore never be given as pill or powder. The sodium salt and salicin are much less irritating. Gastroscopic observations have shown that aspirin in contact with the mucosa does produce an inflammatory reaction, even to the extent of hæmorrhage, in 80 per cent. of cases. This is not dependent upon free salicylic acid. The glucoside salicin is in the bowel converted into glucose and saligenin, and this is further decomposed into salicylic acid, salicyluric acid, and salicylous acid.

Absorption. Salicylic acid, whether taken directly or formed in the bowel from the decomposition of salicin, is rapidly absorbed in spite of its insolubility, and therefore it is probably taken up as sodium salicylate; anyhow, this is the form in which it circulates in the blood.

Liver. Sodium salicylate increases the amount and the solids of the bile by a specific action on the liver cells. The fluid is increased more than the solids, thus the bile is rendered more dilute.

Heart. Salicylic acid in small doses increases the rate of the pulse from stimulation of the cardiac muscle and the blood pressure from stimulation of the vaso-constrictor centre. Large doses depress both.

Respiration. Moderate doses have very little effect on respiration. Toxic doses strongly depress it.

Temperature. In medicinal doses salicin and salicylic acid have no influence on the temperature of man, in toxic doses they slightly lower it ; but they readily depress a febrile temperature, and are therefore called **antipyretics.** Their action on the skin is not sufficient to explain the whole of the fall.

Nervous system. We know little of the effect of salicylic acid on the individual parts of the nervous system. The clinical symptoms known as salicylism will be described presently.

Skin. It causes flushing of the skin and increased sweating by its central action.

Kidney. Salicylic acid escapes chiefly through the kidneys. It to a much less extent also leaves the body by the sweat, the saliva, the bronchial secretions, and the fæces. It appears in the urine very soon after its ingestion (in from 10 to 30 minutes), and half of it is eliminated in 2 hours. It is excreted as salicyluric acid and sodium salicylate, which is split up by the phosphoric acid in the urine, yielding salicylic acid. The dark greenish colour of the urine sometimes seen is due to small quantities of either indican or pyrocatechin. Occasionally salicylic acid causes hæmaturia, due to congestion of the kidneys. It renders the **urine antiseptic,** and the salicyluric acid in that fluid will reduce Fehling's solution. The urine of patients taking it gives a **purple colour** with **perchloride of iron.**

Metabolism. Salicylates **increase protein metabolism,** hence the total nitrogen and sulphur in the urine are increased. The quantity of uric acid is particularly great. They also lower the prothrombin level of the blood. This is due to the action of some degradation product of salicylate on the liver. Large doses may thus give rise to bleeding (*vide infra*). Salicylates have no effect on blood-clotting *in vitro.* An appreciable effect on prothrombin level is likely to be produced by the administration of 4 grammes salicylate daily. The change will be noted on the third day. Menaphthone 1 mg. will counteract the effect on clotting of 1 G. salicylate *if given prophylactically.* Salicylates produce acidosis owing to an increase in fixed acid arising from the presence of lactic and phosphoric acids resulting from altered metabolism.

Salicylism. In some persons to whom salicylic acid or its salt is given symptoms occur to which the above name has been applied. They are very like those produced by quinine. The commonest symptom is deafness, which is often accompanied by ringing in the ears. Headache is also frequent. The administration of the drug is usually stopped when these symptoms show themselves, but if it is continued the patient becomes violently delirious, there is nausea and vomiting, the face is flushed, and the other symptoms increase in severity. The pulse falls in both frequency and force, it becomes irregular, epistaxis is common, and hæmorrhages from other parts of the body have been recorded, such as hæmaturia and retinal hæmorrhage. Albuminuria without hæmaturia has been observed. One of the rarest symptoms is erythema or urticaria. Very large doses may cause the breathing to become weaker, and death may take place either from cessation of the heart or of the respiratory movements. Many of these symptoms are due to acidosis and can be avoided by the administration of bicarbonate.

Therapeutics

External. The ointment may be used when an antiseptic stimulating ointment is required. Strong applications of salicylic acid are useful for removing excess of epidermis, warts, or corns. Salicylic acid 11 parts, Extract of Cannabis Indica 2 parts, Collodion flexile 87 parts, form a remedy (commonly known as green solution) for soft corns. Powdered salicylic acid mixed with starch or chalk may be employed to check profuse perspiration of the feet and axillæ.

Methyl salicylate is useful when rubbed in for chronic rheumatism: an ointment of 1 in 2 to 4 of lanolin may be used, and a liniment (Linimentum Methylis Salicylatis B.P.C.) containing methol, 5; oil of eucalyptus, 10; essential oil of camphor, 25; methyl salicylate to 100, is of value when painted on the painful parts and covered with flannel or gutta percha.

Internal. Salicylic acid is a specific for **rheumatic fever**; it lowers the temperature, lessens the swelling, leads to a rapid cessation of pain, but does not diminish the liability to pericarditis and other complications. It must be given well diluted to prevent dyspepsia. The sodium salt is often preferred as being the most soluble, but in order to diminish the risk of salicylism it should be prepared either from pure artificial or from natural salicylic acid. It should be given in conjunction with twice as much sodium bicarbonate to lessen gastric irritation and reduce the tendency to acidosis. If the attack is severe, 20 grains every two or three hours should be given for the first twelve or twenty-four hours: then, if the patient is doing well, the frequency of the dose may be gradually diminished, but it should be continued four-hourly for ten days after the temperature is normal and the pain has ceased. Salicin is not so powerful as sodium salicylate, but it is said to be less depressant than the synthetic acid.

These preparations are analgesic and often employed in the treatment of chronic rheumatism; acetyl salicylic acid is largely used for these disorders. With some persons it acts as an hypnotic.

Aspirin not only relieves the **pain,** but also the stiffness of **fibrositis.** The effect passes off in three to four hours.

Calcium aspirin is soluble and greatly to be preferred to the sodium salt because it will not give rise to gastritis. It is unstable in solution.

Salicylic acid or salicin may produce a fall of temperature in any fever, but not to the same degree as in rheumatic fever.

Varicose veins. Solutions of 20, 30, or 40 per cent. sodium salicylate are injected in doses of 6, 4 and 2 c.c.

respectively into varicose veins. Thrombosis occurs as the result of irritation of the endothelium. Intense pain is often experienced for thirty seconds after the injection.

BENZOIN

Benzoinum (**B.P.**). A balsamic resin obtained from the incised stem of *Styrax Benzoin.*

Composition. The chief constituents are—(1) *Benzoic acid* (*see below*), 12 to 20 per cent. (2) Cinnamic acid, $C_9H_8O_2$, a trace. (3) Resins. (4) Volatile oil.

Preparations (**B.P.**)

1. **Adeps Benzoinatus.** Benzoinated lard. Benzoin, 2 per cent.

2. **Tinctura Benzoini Composita.** *Synonym.* Friars' balsam. Benzoin, 100; storax, 75; balsam of tolu; aloes; alcohol (90 per cent.), to produce 1000. Macerate.

Dose, 30—60 min. 2—4 ml.

Acidum Benzoicum (**B.P.**). Benzoic Acid. $C_6H_5{\cdot}COOH$.

Source. From benzoin by sublimation or synthetically from toluene, hippuric acid, and other organic compounds.

Characters. Light, almost colourless, crystalline plates or needles. *Solubility:* 1 in 450 of cold water, 1 in 12 of boiling water, readily in solutions of alkalies.

A constituent of Tinctura Opii Camphorata.

Ammonii Benzoas (**B.P.C.**). $NH_4C_7H_5O_2$.

Source. Neutralize benzoic acid with ammonia, and evaporate.

Characters. Colourless laminar crystals, with odour of benzoic acid. *Solubility:* 1 in 6 of water, 1 in 22 of alcohol (99 per cent.).

Dose, 5—15 gr. 0·3—1 G.

Sodii Benzoas (**B.P.**) $NaC_7H_5O_2$.

Source. Neutralize a solution of benzoic acid with sodium carbonate, and crystallize.

Characters. A crystalline or amorphous white powder. Taste sweetish, alkaline. *Solubility:* Easily in water, 1 in 24 of alcohol (90 per cent.).

Dose, 5—30 gr. 0·3—2 G.

Action

As far as is known, the action of benzoic acid, its salts, and benzoin is the same.

External. Benzoic acid and its salts are antiseptic.

In a concentrated form it is a stimulant and irritant when applied to the skin.

Internal. The acid and its salts are somewhat similar in action to the salicylates. Thus they lower the temperature and in large doses produce nausea and vomiting. Disorders of hearing do not occur, and only rarely is evidence of central nervous stimulation to be found. The rapid conversion to hippuric acid is largely responsible for the slight action. This happens by combination with a molecule of glycine, $C_6H_5 . COOH + NH_2 . CH_2 . COOH = C_6H_5 . CO . NH . CH_2 . COOH$ (hippuric acid) + H_4O. The conversion takes place in the liver. The hippuric acid in the urine **renders alkaline urine acid,** and it stimulates and disinfects the urinary mucous membrane.

Benzoic acid has been claimed as an expectorant, but it is unlikely to have any general effect on the body owing to rapid conversion to hippuric acid.

Therapeutics

External. Friar's balsam is seldom used now as a dressing for wounds. It is antiseptic and possesses a stimulating effect. Benzoinated lard is a common basis for ointments ; the benzoin prevents the decomposition of the lard.

Internal. *Lungs.* Benzoin, benzoic acid and its compounds are employed as expectorants in cases of bronchitis. The vapour from a mixture of a pint of water at 52° C. and a fluid drachm (4 mils) of compound tincture of benzoin is inhaled for bronchitis and laryngitis.

Urinary organs. Benzoic acid is valuable for acidifying the alkaline decomposing urine of cystitis. Ammonium and sodium benzoate are much more soluble than benzoic acid and are to be preferred to it. Spirit of chloroform covers the taste.

Benzoic acid and sodium benzoate are used in the performance of a liver function test. The best method is to give intravenously 1·7 G. benzoic acid in 20 ml. sterile water. The percentage which is excreted as hippuric acid at 1 and 2 hours in the urine is estimated. Normal figures are 35 per cent. or over at 1 hour ; 65 per cent. or more in the second hour.

Benzyl Benzoas (B.P.). Benzyl Benzoate. $C_6H_5 \cdot COOC_7H_7$.
CHARACTERS. Colourless crystals or oily liquid. *Solubility:* Freely in alcohol and ether.

Dose (not official), **5—8 min.** **0·3—0·5 ml.**

Action

Benzyl benzoate relaxes spasm in unstriped muscle by direct action. It is a parasiticide exerting a lethal effect on *Sarcoptes hominis.*

Therapeutics

Given in capsules or as an emulsion it is used in the treatment of various forms of colic and in asthma. It has also been extensively employed for whooping-cough. For this action it is inferior to the nitrites and the belladonna alkaloids.

It is of great value in the treatment of **scabies.** An emulsion is made of equal parts of benzyl benzoate, industrial spirit and soft soap. This is applied to the skin and allowed to dry. A further application is then made. The clothes are then resumed. A bath is taken the next day, and clean clothes put on. It has the advantage over sulphur in its lack of odour and smaller tendency to cause dermatitis. It may irritate the scrotum.

GROUP XX

Sulphonamides

The "*sulphonamides*" used in medicine are para-aminobenzenesulphonamide and certain derivatives of it. There are many other compounds containing the sulphonamide (SO_2NH_2) radical known to chemists which have no therapeutic application. Since *p*-aminobenzenesulphonamide is the amide of sulphanilic acid the designation **sulphanilamide,** which is accurate and brief, has generally been adopted for it, and no other name should be used. The derivatives of sulphanilamide fall into two groups. In the first, a hydrogen atom in the amino (NH_2) group has been substituted and in the second substitution has taken place in the amide hydrogen. To the first group belong sulphonamidochrysoidin (Prontosil rubrum), azosulphamide (Prontosil soluble), benzylsulphanilamide (Proseptasine), and various derivatives more soluble than sulphanilamide itself such as Soluseptasine. The second group includes sulphanilyldimethyl sulphanilamide (Uleron), sulphapyridine, sulphathiazole, sulphacetamide, sulphadiazine, and sulphaguanidine. It is most important that the nomenclature employed for these substances should be accurate, and a distinction drawn between the full chemical name of a compound, its recognized non-proprietary name and one or more trade names for proprietary brands. The term **sulphonamide** is a generic name covering all members of the group, and it is meaningless therefore to refer to treatment by *sulphonamide* since it is not the name of a substance. The use of the word *sulphanilamides* as a generic name should be avoided.

Sulphonamide therapy dates from February, 1935, when Domagk announced that a red azo dye-stuff containing a sulphonamide group, namely, 4-sulphonamido-2 : 4-diaminoazobenzene, was active in experimental hæmolytic streptococcal infections in mice. This compound was subsequently called Prontosil, and later Prontosil rubrum to distinguish it from other compounds to which the same trade name has been applied. Later in the same year, the Tréfouëls, Nitti, and Bovet made a discovery of great importance that the dye-stuff was split at the azo linkage with release of para-aminobenzenesulphonamide to which its activity was due. No further reference will be made to the azo sulphonamides as they cannot but be regarded now as of historic interest only. All derivatives of sulphanilamide of the first group act in the same way, namely, by virtue of the sulphanilamide released from them in the body tissues. Their activity and toxicity will therefore be essentially the same as that of sulphanilamide itself. Compounds of the second class, on the other hand, are active *per se* and are not broken down with release of sulphanilamide. They tend to have a greater degree of activity than sulphanilamide. Activity in bacterial infections is not confined to compounds containing the sulphonamide group as other sulphur compounds, notably the sulphones, are active, and they are chemically unrelated to the sulphonamides.

(Structural formulæ are to be found in the B.P.)

Sulphanilamidum (B.P.). Sulphanilamide. *Unoff. Synonyms.* Sulphonamide P and P.A.B.S.

Trade names include Colsulanyde, Prontosil album, Prontylin and Streptocide.

Composition. Para-aminobenzenesulphonamide.

Characters. Colourless crystals or a white crystalline powder; odourless; taste, slightly bitter with a sweet after-taste. Soluble in 250 parts of water at 15·5°, in 170 parts of water at 20°, in 115 parts of water at 25°. Sparingly soluble in alcohol (95 per cent.). Insoluble in ether, in chloroform and in benzene. Melting-point 164·5°–166·5°.

Dose, 30 gr.—2 G. initial.
15 gr.—1 G. subsequent, four-hourly.

Benzyl-sulphanilamide. *Tr. Name.* Proseptasine (M. & B. 125).

Composition. Para-benzylaminobenzenesulphonamide.

Characters. A white crystalline, odourless, tasteless powder. Solubility in water 1 in 25,000. Melting-point 174° to 178°.

Soluseptasine (trade name).

Composition. Disodium-p-(γ-phenyl-propylamino)-benzenesulphonamide-α-γ-disulphonate.

Characters. A white crystalline powder soluble in water. Used in the form of a 20 or 10 per cent. solution for parenteral administration.

Sulphacetamidum (B.P.). Sulphacetamide. *Tr. Name.* Albucid.

Characters. A white or creamy-white odourless, tasteless crystalline powder. Soluble in water (1 in 150 at 20°), alcohol (95 per cent.) (1 in 15), and acetone (1 in 7).

Composition. Para-aminobenzenesulphonacetamide.

Sulphacetamidum Sodium (B.P.). Soluble sulphacetamide. *Tr. Name.* Albucid Soluble.

Characters. A white microcrystalline powder soluble in water (1 in 2·5) and sparingly soluble in alcohol (95 per cent.) and acetone. The aqueous solution is neutral to litmus solution.

Composition. The sodium salt of sulphacetamide.

Sulphapyridina (B.P.C.). Sulphapyridine. *Tr. Name.* Dagenan. (M. & B. 693).

Characters. A white or creamy-white crystalline powder with a slightly bitter taste. Solubility in water (1 in 4000).

Composition. 2-sulphanilylamino-pyridine or 2-(*p*-aminobenzenesulphonamido) pyridine.

Dose, 8—30 gr. 0·5—2 G.

Sulphathiazolum (**B.P.**). Sulphathiazole. *Tr. Name.* Thiazamide (M. & B. 760).

CHARACTERS. A white crystalline powder practically odourless and tasteless. Solubility in water at 20° (1 in 2500) slightly soluble in alcohol (95 per cent.). Melting-point, 200° to 203·5°.

COMPOSITION. 2-sulphanilylamino-thiazole or 2-(*p*-aminobenzenesulphonamido) thiazole.

Dose, 30 gr.—2 G. initial.
15 gr.—1 G. subsequent, four-hourly.

Sulphathiazolum Sodium (**B.P.**). Soluble sulphathiazole. *Tr. Name.* Thiazamide Sodium (M. & B. 760 soluble).

CHARACTERS. A white or creamy-white crystalline powder, practically odourless. Solubility in water approximately 1 in 3.

COMPOSITION. The sodium salt of sulphathiazole.

Dose, as for Sulphathiazole.

Preparation (**B.P.**)

Injectio Sulphathiazoli Sodii.
Dose, 8—30 gr. 0·5—2 G.—by intravenous injection.

Sulphadiazina (**B.P.**).

CHARACTERS. A white crystalline powder. Solubility in water at body temperature 12·3 mgs. per 100 c.c.

COMPOSITION. 2-sulphanilylamino-pyrimidine or 2-(*p*-aminobenzenesulphonamido) pyrimidine.

Dose, 30 gr.—2 G. initial.
15 gr.—1 G. subsequent, four-hourly.

Sulphadiazina Sodium (**B.P.**).

Sodium Sulphadiazine is used for intravenous injection. *Solubility.* 1 in 2.

Dose, as for Sulphadiazine.

Preparation (**B.P.**)

Injectio Sulphadiazinæ Sodii.
Dose, 8—30 gr. 0·5—2 G. by intravenous injection.

Sulphaguanidina (**B.P.**).

CHARACTERS. A white crystalline powder soluble in water at body temperature in a concentration of 200 mgs. per 100 c.c. Melting-point, 142·5° to 143·5°.

COMPOSITION. Para-amino-N-guanylbenzenesulphonamide or sulphanilylguanidine.

Dose, 30—60 gr. 2—4 G.

Sulphamezathine = sulphadimethylpyrimidine.

CHARACTERS. A white crystalline powder. Solubility 190 mgms. per 100 c.c. at body temperature.

Dose, 15 gr.—1 G. six-hourly.

Succinylsulphathiazolum (B.P.). Succinylsulphathiazole.

CHARACTERS. A white crystalline powder. Solubility 70 mg. per 100 c.c. of water as body temperature.

STRUCTURAL FORMULA.

Dose 45—90 gr. 3—6 G.

Sulphamerazine.

A pyrimidine derivative of sulphanilamide of high solubility.

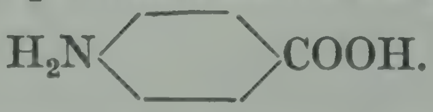
Dose, 15 gr.—1 G. six-hourly.

Sulphonamide Preparations (B.P.).

There are official tablets of Sulphadiazine, Sulphaguanidine, Sulphanilamide, Succinylsulphathiazole and Sulphathiazole. In each case the tablet contains 8 gr.—0·5 G. of the drug.

Action

The sulphonamides are absorbed from the alimentary tract and diffuse throughout all body tissues and fluids. At suitable concentrations a bacteriostatic action is exerted on invading micro-organisms susceptible to the action of the drug. Sulphonamides do not neutralize toxins or stimulate antibody production or phagocytosis. They bring about diminution in the rate of growth of bacterial cells by interfering with their metabolism, thereby enabling the infection to be overcome by the natural defence mechanism, including such processes as phagocytosis and lysis. In much higher concentrations than can be secured *viâ* the blood stream, such as occur in urine during elimination and in wound fluid and the wound wall after implantation, an actual bactericidal action can be exerted. The bacteriostatic action of sulphonamides is inhibited in the presence of protein breakdown products, including peptone and pus. Still more effectively the action of sulphonamides can be neutralized by low concentrations of p-aminobenzoic acid,



Now this substance is essential for the growth of bacteria. The bacterial enzyme-system which uses it will also take up sulphonamides because of their chemical similarity to it. This must block the enzyme-system from receiving the p-aminobenzoic acid necessary for bacterial growth and thus it is that the sulphonamides are effective.

It is of practical interest to note that procaine, which is a complex ester of p-aminobenzoic acid, will on that account tend to neutralize the action of the sulphonamides and will also give their colour reactions on which qualitative estimation depends. The two drugs should not be used together, therefore, 1 part of p-aminobenzoic acid actually requires 1,600 parts of sulphanilamide to neutralize it. Smaller quantities are needed of sulphaguanidine (1,000), sulphapyridine and sulphadiazine (100) and sulphathiazole (36).

Sulphonamides interfere with the nutrition and growth of the bacterial cell by interfering with the function of bacterial enzymes.

Activity. Pathogenic bacterial organisms vary in their susceptibility to the action of sulphonamides and these drugs vary in their degree of activity. Pneumococci, for example, are more resistant than hæmolytic streptococci and sulphanilamide has a degree of activity sufficient to enable it to prove effective in the treatment of hæmolytic streptococcal infections and less so in meningococcal infections but not in pneumococcal infections. Sulphapyridine, which is a much more active drug, is sufficiently active to be effective in pneumococcal infections. It follows that sulphapyridine is much more active than sulphanilamide on hæmolytic streptococci, but it is not necessarily the drug of choice for the treatment of hæmolytic streptococcal infections, as other considerations are involved in selecting the most appropriate drug for the treatment of a given infection. Sulphathiazole and sulphadiazine and sulphamerazine are effective against all these organisms and also staphylococci. The conception that certain sulphonamides have a specific action on certain organisms is erroneous. Their therapeutic activity depends upon the degree of dissociation they undergo in solution and is probably due to the anion. Sulphathiazole is dissociated 3,000 times more than sulphanilamide. It does not follow that the degree of therapeutic effect exerted by different sulphonamides in the treatment of an infection will run parallel with the absolute activity on the organism as measured in the laboratory, as the therapeutic activity will be influenced by the rates of absorption and elimination, degree of acetylation, solubility in blood and other body fluids as well as additional factors.

With any given species of organism considerable variation in sulphonamide susceptibility may be found among different strains, but roughly some common pathogens could be arranged in the following order of decreasing sulphonamide susceptibility.

Hæmolytic streptococci, *Hæmophilus ducreyii*, meningococci, gonococci, *Streptococcus viridans*, pneumococci, the coliform organisms, dysentery bacilli, certain clostridia, *Staphylococcus aureus*, *Hæmophilus influenzæ*, *Klebsiella pneumoniæ* (Friedländer's pneumobacillus), *Streptococcus fæcalis*, the genus brucella.

Sulphonamides have no action on anaerobic streptococci and are of little value for the treatment of the enteric fevers. They have little or no action in virus infections.

Absorption, Distribution, Excretion and Metabolism.—Most sulphonamides are rapidly absorbed from the alimentary tract, the rate being dependent chiefly on the solubility of the compound. The absorption of sulphanilamide, sulphathiazole, sulphamezathine, sulphamerazine, sulphadiazine, and sulphapyridine decreases in that order. Not all soluble sulphonamides are rapidly absorbed, however, and sulphaguanidine and succinyl sulphathiazole were introduced as the result of a search for fairly soluble sulphonamides which were poorly absorbed and which, therefore, could give rise to high concentrations in the alimentary canal for the treatment of infections largely localised here, such as bacillary dysentery, the enteric fevers, and cholera. About 50 per cent. of sulphaguanidine and 5 per cent. of succinyl sulphathiazole are absorbed. Absorption chiefly takes place in the upper part of the small intestine. It also occurs from the stomach and colon. Oral administration should be employed when possible, and parenteral administration used when necessary as a substitute or to supplement it. Absorption from the rectum is poor and rectal administration has little or no place in therapeutics. After absorption diffusion takes place to all body-fluids and tissues, the ratio of the concentration in the peripheral blood to various fluids and tissues varying with different drugs. The distribution of sulphanilamide, for example, is more even than that of the other compounds. The concentration reached in bone and fat is less than in other tissues. Sulphapyridine accumulates in the liver in twice its concentration in the blood. Whereas sulphanilamide reaches the C.S.F. in the same concentration as in the blood, sulphapyridine, sulphadiazine, and sulphathiazole appear in relatively smaller concentrations in descending order. They pass through the placenta into the fœtal circulation. All these drugs appear in the bile in the same concentration as in the blood. The concentration of bile in the gall-bladder raises that of the sulphonamides.

The sulphonamides are chiefly excreted through the kidneys and the rate of excretion is rapid although variable with different compounds. Sulphathiazole is excreted more rapidly than sulphapyridine, and this is the chief reason why it is impossible by oral administration of the former to secure the high blood levels which may be obtained with sulphapyridine. After a single oral dose the maximum concentration in the blood is reached at the end of about three hours, after which it falls. The concentration in the blood and other body fluids, and in tissues, can be determined by colorimetric tests.

After absorption a proportion of the compound is converted to an acetyl derivative by replacement of one hydrogen atom of the amino group with an acetyl radical. This acetylation takes place chiefly in the liver and the degree of acetylation varies within wide limits in different patients and in a given patient from day to day. The acetyl or conjugated form, as it is also called, is inactive. Many of these acetyl derivatives are less soluble than the parent compounds and thus tend to crystallise out during excretion through the kidneys. This may give rise to hæmaturia or anuria. The excretion of sulphamezathine and sulphamerazine is slow and thus a high blood concentration can be maintained with less frequent administration than is necessary for the other sulphonamides. The concentration of sulphonamides is greatly raised in the process of excretion so that 100 mg. or more may be present in 100 c.c. urine. The colorimetric estimation of sulphonamides in body fluids may be extended to the determination of the proportion of acetyl derivative present by its hydrolysis to the free form.

Administration. In addition to administration by mouth, sulphonamides are given by subcutaneous, intramuscular and intravenous injection, and by drip infusion intravenously or subcutaneously. Intraperitoneal administration is sometimes used and application to wounds is employed. There is no indication in therapeutics for the intrathecal administration of sulphonamides. Neutral soluble derivatives of sulphanilamide are available, such as Soluseptasine, and of soluble preparations of sulphanilamide derivatives of the second group, sodium sulphacetamide yields a neutral solution. The sodium salts of sulphapyridine, sulphathiazole, and sulphadiazine, however, yield highly alkaline solutions. These must never be given subcutaneously, and the intramuscular route should be avoided when possible. Sodium sulphapyridine solution may, however, be given intramuscularly if great care be taken with the technique to avoid leakage into the subcutaneous tissues with resulting necrosis: and damage to nerve structures from improperly given injections has resulted in wrist drop and in foot drop. The dosage of any sulphonamide for parenteral administration is the same as when the oral route is used. Rectal administration is unsatisfactory.

General Principles of Sulphonamide Therapy. These drugs are of most value in the treatment of infections by organisms of an invasive character undergoing rapid multiplication, which produce as a consequence infections running an acute course. They are of less value in infections by organisms of low virulence, producing infections of a subacute or chronic character, particularly when localized in nature. They are more effective at high body-temperatures. The action of the sulphonamides is quantitative as well as qualitative and other things being equal, the higher the number of organisms the greater the concentration of the drug which will be required. Organisms rapidly acquire the power to resist the inimical action of the drug and develop a condition known as drug fastness or drug resistance. In the treatment of acute infections a technique is required which differs from the principles governing the use of any other class of drugs, and it is essential that the fundamental principles should be followed. A blood concentration adequate for bacteriostasis of the invading organism must be secured rapidly by high initial dosage, and this must be followed by a smaller dose at regular intervals of about four hours to maintain the blood level constant at the figure secured. Treatment must be begun in acute infections as early as possible. The suggestion which has sometimes been made that there should be a deliberate delay in instituting treatment cannot be too strongly condemned. It must be emphasized also how essential it is to follow these principles, and in an acute infection it would be far better not to employ a sulphonamide at all rather than use it on the wrong lines. The prescribing of one $\frac{1}{2}$-grm. tablet of sulphapyridine, say, three times a day in pneumonia is not merely likely to be useless, it can be harmful and positively dangerous. Once drug fastness has been established subsequent raising of the dose will be useless. In an acute infection the manner in which chemotherapy is employed during the first twenty-four hours determines the outcome. If a response is going to be obtained it will be obtained early, and in the absence of a response after forty-eight hours of treatment, administration should not be continued without investigating the reason for the failure.

These principles apply less to subacute infections and usually do not apply at all in chronic conditions.

Reactions. All the sulphonamide compounds in use affect the metabolism of normal body cells as well as that of bacterial cells. Thus they interfere with the working of the cells of any tissue. Various reactions may arise as a result of toxicity or hypersensitivity. **Cyanosis** is common with sulphanilamide, and is usually associated with the presence in the erythrocytes of methæmoglobin or sulphæmoglobin. The formation of methæmoglobin from hæmoglobin is reversible, and *methæmoglobinæmia may be abolished or prevented by the administration of methylene blue.* Sulphæmoglobin, however, cannot be converted into hæmoglobin, so it remains during the life of the erythrocyte. The cyanosis of sulphonamide therapy rarely gives rise to any symptoms of oxygen want, and in a patient who is not markedly anæmic it may be ignored. It has been suggested that sulphur-containing foodstuffs or drugs and saline aperients are contra-indicated during sulphonamide therapy as they conduce to the formation of sulphæmoglobin. This is probably not the case, but sulphæmoglobincythemia is exceptionally rare with sulphanilamide derivatives of the second group (sulphapyridine, sulphathiazole, etc.) so that with these derivatives the question does not in any case arise. Central nervous system manifestations are common, and they result in disturbance of the alimentary tract or mental symptoms. Sulphapyridine exhibits the greatest tendency to produce reactions of this type, and **nausea** and **vomiting** frequently introduce a difficulty in the use of this drug. There is no effective method of overcoming the trouble. The tablets should be crushed to a fine powder which is administered suspended in milk or other suitable medium, and it is an advantage to divide the dose into a number of parts, given at intervals. If a patient vomits shortly after the administration of sulphapyridine, the dose should be repeated after the patient has settled down for about fifteen minutes. The administration of 6–10 minims of Tr. opii half an hour before each dose of sulphapyridine may prevent vomiting by virtue of its action on the medullary centres. Should vomiting continue to be troublesome it may be necessary to have recourse to parenteral administration of the sodium salt, not because this will prevent vomiting but in order that an adequate blood level can be obtained. In many cases it will be necessary to change to sulphathiazole, sulphanilamide or another appropriate compound. Sulphamezathine and sulphadiazine are more soluble than sulphapyridine and do not cause vomiting. They are probably as efficient therapeutically. Headache, giddiness, tinnitus, confusion and depression, more common with sulphapyridine, are frequently troublesome, and at times the patients may appear delirious or intoxicated or the condition may simulate an acute psychosis. These effects usually subside rapidly on withdrawal of the drug, although they may persist for varying periods.

Drug **pyrexia** is commonly encountered, and it is less common with sulphapyridine. It usually appears at the end of a week's administration, and it may be necessary to differentiate drug pyrexia from a rise in temperature due to a recrudescence or extension of the infection. A febrile reaction usually precedes the appearance of drug **rashes.** The latter may be very varied in their morphology, being commonly morbilliform or scarlatiniform, and they may simulate any of the exanthemata completely. The eruption may be urticarial, angio-neurotic œdematous, or bullous. Dermatoses are commoner with sulphathiazole than the other drugs, and this compound alone gives rise to an eruption which has the appearance of erythema nodosum. It is frequently accompanied by **conjunctivitis** and **scleritis,** and the not uncommon occurrence of **painful joints** may be diagnostically misleading unless the history of having taken sulphathiazole is borne in mind. The majority of skin lesions arise as a sensitization phenomenon at about the tenth day of therapy, and in common with other forms of sensitization reactions the patient remains sensitized for months, probably for the rest of his life. Any sensitized patient immediately shows some reaction if the drug is again administered. Sometimes skin eruptions arise as **photosensitivity**, porphyrins being the light sensitizing agents. The actinic dermatitis is sometimes associated with stomatitis and with mental changes, and this together with the porphyrinuria forming a **pellagra-like syndrome** has suggested the use of nicotinic acid, which has proved very effective in the treatment of this pellagroid state. It is possible that these pellagroid symptoms are due to conditioned nicotinic acid deficiency produced by partial sterilization of the gut. This is especially likely to occur with succinyl sulphathiazole. The loss of microbial activity would arrest the biosynthesis of vitamin B (*q.v.*). It is more probable that the sulphonamides interfere with the respiratory enzyme systems with which the B vitamins are deeply involved. Symptoms of nervous disease could thus be explained. Nicotinic acid has also been found useful in ameliorating a number of the other unpleasant sequelæ and side effects of sulphonamide therapy, and it should be given in a dosage of not less than 50 mgs. four times a day. Slight degrees of **hepatitis** are common as a result of sulphonamide therapy, but fortunately severe liver damage is rare. Acute toxic hepatitis has a high mortality rate, and the jaundice and other symptoms may not appear until the course of treatment by the drug has been completed. In some half of the cases of severe liver damage there is an accompanying dermatitis, usually severe and proceeding to generalized exfoliation. Acute hæmolytic anæmia is also a sensitization phenomenon, but it appears during the first three days or so of treatment. It is frequently accompanied by leucocytosis or hyperleucocytosis. Varying degrees of leucopenia are common during the first few days of sulphonamide therapy and are rarely significant. Leucopenia occurring after the tenth day is, however, dangerous and may be the first sign of an impending **agranulocytosis.** In treating an acute infection a response should have been obtained early if therapy was employed on the correct lines so that the danger of agranulocytosis should rarely arise. Complications may occur in the urinary tract from **precipitation of**

crystals in the renal tubules or pelves and in the ureters. As a consequence there may be hæmaturia, a diminished flow of urine into the bladder or complete blockage of the ureters. This reaction does not occur with sulphanilamide, but it can occur with sulphapyridine, sulphathiazole, sulphadiazine and sulphamerazine (seldom). It will not arise if the urine be kept alkaline. The most important precaution to take during treatment by these drugs is the maintenance of a high fluid intake. Only in this way can urolithiasis be prevented. A watch should be kept on the urine both as regards character and quantity and a diminution in the twenty-four hour output is the most valuable warning sign of urinary tract complication. **Peripheral neuritis** is a rare complication of sulphonamide therapy. Also rare are splenomegaly and hepatomegaly. In addition to the blood dyscrasias already mentioned, **thrombocytopenia** leading to purpura and other hæmorrhagic states may occur. On the occurrence of reactions during sulphonamide treatment the decision has to be made as to whether administration of the drug must be discontinued. If the patient's condition permits it administration should be stopped in all cases and fluids forced to hasten elimination. Dermatoses of the sensitization type usually disappear with continued administration. Acute hæmolytic anæmia responds readily to blood transfusions. Urolithiasis requires cessation of administration and the forcing of fluids, but if the ureters are blocked the passage of intraureteric catheters may be needed.

Therapeutics

Sulphapyridine is no longer used because of the intense depression and nausea it produces.

Dosage. No precise dosage for the different sulphonamides can be laid down, as this will vary with the nature and severity of the infection and other factors. In acute infections a useful general rule, however, for the twenty-four hour quantity is 1 gramme per 20 lbs. body weight in adults, 1 gramme per 10 lbs. body weight in children, and 1 gramme per 5 lbs. body weight in infants. This twenty-four hour quantity is divided into six equal four-hourly administrations, the first dose quadrupled or the first two or three doses doubled or trebled. Sulphamerazine and sulphamezathine which are absorbed readily and excreted slowly can be given six-hourly after the initial loading dose. The acetyl derivative is more soluble than that of sulphadiazine, but it may nevertheless cause hæmaturia. They readily produce a blood concentration of 16 mg. per 100 c.c.

In infections by strains of **hæmolytic streptococci** belonging to Lancefield's group A sulphanilamide is the drug of choice. Erysipelas responds readily. In septicæmia and meningitis blood levels of 10–15 mgs. must be secured rapidly and maintained until there is a response.

In **meningococcal infections** sulphanilamide, sulphathiazole, sulphadiazine or sulphamerazine may be used. Cerebrospinal fever responds readily, and the effect in chronic meningococcal septicæmia is dramatic. In fulminating meningococcal septicæmia the injection of sodium sulphathiazole or sulphadiazine should be used. Cortical hormone should be administered four-hourly by intramuscular injection if symptoms of shock indicate hæmorrhage in the adrenal cortex. The results of investigations suggest that sulphathiazole and sulphadiazine are the most active sulphonamides for use in cerebrospinal fever.

In **gonococcal infections** the activity of sulphanilamide is inadequate and sulphathiazole should be used. For acute gonoccocal urethritis various schemes of sulphathiazole dosage are used, a common practice being to give five doses each of 1 G. daily, continuing until 25 G. have been given.

Gonococcal **ophthalmia neonatorum** may be rapidly cured in the vast majority of cases and 0·5 grm. per 15 lb. body weight of sulphathiazole three-hourly for the first twenty-four hours followed by less frequent administration is an appropriate dosage. Acute gonococcal arthritis and iritis respond readily, but in the chronic forms chemotherapy is only useful as an adjuvant to local measures aimed at opening and draining the deep foci of infection in the genito-urinary tract.

In **vulvo-vaginitis** of girls rapid improvement and permanent cure follows the use of sulphathiazole in the majority of cases. A customary dosage is 0·25 G. four or five times a day.

In **pneumococcal pneumonia** a common dosage of sulphathiazole in adults is two or three doses of 2 G. followed by 1 G. at four-hourly intervals or one dose of 4 G. followed by 1 G. as above. The interval may be six hours for sulphamezathine. Approximately twice this amount should be given in **pneumococcal meningitis** and peritonitis, and in these conditions parenteral administration of the sodium salt will be particularly valuable. Sulphamezathine or sulphadiazine are used more now in this disease because depression and vomiting are rarer. Sulphamerazine in an initial dose of 3 G. followed by 1 G. every six or eight hours is claimed to be equally effective.

Acute or subacute *Bacillus coli* cystitis or **pyelitis** respond to sulphanilamide and other sulphonamides. In chronic cases no permanent effect will be obtained if there is some underlying disease of the urinary tract requiring treatment. Chronic bacilluria may, however, be kept in check by a very small dosage given over long periods. The high concentration on excretion allows of smaller doses, *e.g.* 3 G. a day, than those required for systemic infections. To reduce the danger of anuria (none with sulphanilamide) fluid intake should be 5 pints and the volume output must be watched for any sign of fall. It is wise to keep the urine alkaline by means of sodium bicarbonate and citrate because this reduces the tendency to precipitation of crystals and it also enhances the action of the sulphonamides by increasing ionization. In the presence of other organisms sulphanilamide may be insufficiently active, and for urinary tract infections generally sulphamezathine is the product of choice. For infections with *Str. fæcalis* calcium mandelate should be used with an acid (pH 5·5) urine.

Chancroid sore or bubo respond readily to sulphanilamide or sulphathiazole, 3 G. daily, and a dusting of sulphanilamide powder should be made on to the ulcer in addition to oral administration.

In **staphylococcal septicæmia** sulphathiazole was the first effective sulphonamide, but a blood level in the region of 15 mgs. per 100 ml. is required, and this is impossible of attainment by oral administration alone. A constant intravenous saline drip containing sodium sulphathiazole is given, or oral administration can be supplemented by intravenous injections. It is essential to treat the infection vigorously in its early stages, as otherwise failure may result due to the development of metastases. Sulphadiazine and sulphamerazine do not present this difficulty and are more used. The results in chronic staphylococcal sepsis tend to be unsatisfactory. Penicillin either alone or in conjunction with a suitable sulphanamide is now employed in acute and chronic forms.

In acute **bacillary dysentery**, whether due to Shiga, Flexner or Sonne strains, the response is usually dramatic. Sulphaguanidine up to 20 G. a day is used. Succinyl sulphathiazole up to 10 G. a day is more active against the coliform bacilli and **Sonne dysentery.** It has been shown that these slowly absorbed drugs are in fact no more efficient than sulphathiazole, sulphamezathine, or sulphamerazine, in the treatment of dysentery.

In chronic **cholecystitis** due to *B. coli*, streptococci, or the typhoid organisms sulphathiazole should be given in doses of 1 G. four-hourly for three weeks at least.

In **brucellosis** sulphonamides are of little or no value, and reports of *alleged cures of undulant fever usually represent errors of judgment.*

Sulphonamide therapy has little influence on the course of typhoid or para-typhoid, but in typhoid bacilluria the urine can usually be sterilized and a trial is justified in gall-bladder carriers.

Of anaerobic bacillary infections there is no evidence that sulphonamides are useful in botulism. As it is possible that sulphonamide therapy is useful in tetanus, it should be employed as an adjuvant to the administration of antitoxin and an attack on the focus, as well as the administration of appropriate narcotic drugs.

A clinical assessment of the value of sulphonamides in gas gangrene is difficult. These drugs are active on *Cl. welchii*, less active on *Cl. septique*, and without activity on *Cl. œdematiens*. For the treatment of **gas gangrene** the more active compounds should be employed in preference to sulphanilamide and energetic treatment is essential, particularly in the acute and fulminating types of gas gangrene. Sulphonamides should naturally be employed in conjunction with surgical measures and the administration of antitoxin.

In subacute and chronic infections sulphonamides are generally of less value than in acute infections. Striking immediate improvement follows the administration of sulphathiazole in subacute infective endocarditis, but the fatal outcome remains uninfluenced by this drug. Penicillin is now used in this disease. In **actinomycosis** both of the jaw and of the abdominal viscera sulphonamides are effective, but as a proportion of abdominal cases tend to relapse it is advisable to continue the administration of small doses for a considerable time as a prophylactic measure. In **lymphogranuloma inguinale** sulphonamide therapy will frequently control the condition. The dose is 5 G. daily for five days and then 3 G. daily for six weeks. The blood picture must be watched.

Some cases of trachoma respond, probably those with secondary bacterial infection.

In dermatology sulphonamides are effective in **pemphigus neonatorum.** Complete remission of symptoms can frequently be secured in **dermatitis herpetiformis** lasting for varying periods. The drugs are less effective in **pemphigus vulgaris,** but varying degrees of improvement are usually secured. In **lupus erythematosus** of the discoid type sulphonamides are frequently effective, but initial treatment must be cautious with small dosage as these patients are particularly liable to drug pyrexia and rashes with focal reactions. A large variety of **pyogenic dermatoses** have been treated both by oral administration and topical application with varying results. A 5 per cent. cream of sulphathiazole should be applied daily for a week only in cases of **impetigo.** This drug or sulphadiazine should be given by mouth for **boils** and the skin protected with sulphathiazole once discharge occurs.

The **topical application** of sulphonamides in the form of powder has a valuable place in surgery for the prevention of wound and burn sepsis and to enable skin grafts to "take." Five to 15 G. of the sulphonamide in powder form are used in **wounds** according to their size, and as sulphanilamide is rapidly absorbed its implantation has to be followed twenty-four hours later by oral administration. The advantage of sulphanilamide for this purpose is that it is soluble and will penetrate. If 3 parts of sulphanilamide be combined with 1 part of sulphathiazole the local concentration will be maintained for a long time (four times). In blood sulphathiazole is about ten times as active as sulphanilamide, but owing to its lower solubility the final action in a wound is about the same. In any case the action of sulphonamide is restricted to the immediate vicinity of where it was deposited. It is likely to be effective prophylactically and therapeutically on relatively superficial wounds not presenting many crevices. Sulphonamides must not be placed near nerve trunks because they cause degeneration of nerve fibres.

By the local use of these drugs **septicæmia** and **gas gangrene** have been greatly reduced.

In **ophthalmia neonatorum** drops of 30 per cent. sodium sulphacetamide should be instilled two-hourly. For **corneal ulcer** 10 per cent. is used.

The **intraperitoneal application** of sulphonamides is now often used after operations on septic conditions within the abdomen. Sulphanilamide is probably the safest drug, for the less soluble ones are apt to form lumps and produce dense adhesions. Although sulphanilamide is absorbed rapidly from the peritoneal cavity producing a therapeutically effective blood-concentration for a few hours only, yet its concentration in the peritoneal exudate falls more slowly. The concentration of the drug in the portal veins is 40 per cent. higher than in the systemic circulation. There is, therefore, increased danger of toxic hepatitis. To avoid this, not more than 15 G. should be used.

Whichever sulphonamide is used it should be introduced as a fine suspension in order to avoid the formation of irritant masses.

Probably sulphanilamide is adequate for prophylaxis and a combination of 3 in 1 with sulphathiazole is best in the treatment of peritonitis.

Whenever sulphonamides are used for local application their sterility should be ensured. Fatal tetanus has already arisen owing to failure to observe this precaution. The spores are probably derived from the packing usually employed.

The application of a sulphanilamide paste or **cream** is gaining popularity in the treatment of **burns.**

Prophylaxis. It is claimed that the use of sulphonamides prophylactically will materially reduce the relapse rate of **rheumatic fever.** Sulphanilamide 0·5 G. twice daily should be given until adolescence.

Prior to operation on the gut **phthalyl sulphathiazole** 10 G. daily may be given. It is not absorbed, and greatly reduces the intestinal flora.

GROUP XXI

Digitalis, Strophanthus, Squill

DIGITALIS

Digitalis Folium (B.P.). Digitalis Leaf. *Synonym.* Digitalis. The dried leaves of *Digitalis purpurea*, the purple foxglove.

Digitalis Præparata (B.P.). Powdered digitalis leaf. The powder must be assayed by the biological assay of powdered digitalis. Strength stated in terms of international standard digitalis powder—0·1 G. has activity described as 1 Unit.

Dose, ½—1½ gr. 30—100 mg.

Composition. The active principles are glucosides, which are hydrolysed by acids with the production of so-called " aglucones " or "genins" (non-carbohydrate), and sugars. Saponins are also present in leaves and seeds, but exert no digitalis effect. The following are the chief glucosides :—

(1) From seeds : Digitalinum verum, $C_{36}H_{56}O_{14}$. Sparingly soluble in water, but present in aqueous extracts because of associated saponins.

(2) From leaves : (*a*) Digitoxin, $C_{41}H_{64}O_{13}$. Sparingly soluble in water ; soluble in alcohol. It is the main active constituent of infusions, the saponins Digitonin and Gitonin holding it in colloidal suspension.

(*b*) Gitoxin, $C_{41}H_{64}O_{14}$. Also insoluble, when pure, in water.

Preparations (B.P.)

1. **Tabellæ Digitalis Præparatæ.** Contain 1 gr. (0·06 G.)·

2. **Tinctura Digitalis.** Digitalis leaves ; alcohol (70 per cent.).

Dose, 5—15 min. 0·3—1 ml.

Digitalis Lanata is another species, the white foxglove. Its active principles are also glucosides breaking up into genins and specific sugars. The most important glucoside is digoxin, which is isomeric with gitoxin. It can be prepared in pure crystalline form, and its purity can therefore be controlled by chemical analysis.

Digoxinum (B.P.). Digoxin.

CHARACTERS. Colourless crystals. *Solubility :* Almost insoluble in water ; soluble in dilute alcohol.

Dose, $\frac{1}{60}$—$\frac{1}{40}$ gr. 1—1·5 mg.—initial dose.
$\frac{1}{240}$ **gr.—0·25 mg.** twice daily—maintenance dose.
$\frac{1}{120}$—$\frac{1}{60}$ **gr. 0·5—1 mg.**—intravenously.

Preparation (B.P.)

1. **Injectio Digoxini.** Contains 1 mg. ($\frac{1}{60}$ gr.) in 20 ml. (300 min.).

Dose, 150—300 min. 10—20 ml. by intravenous injection.

2. **Tabellæ Digoxini.** Each contains 0·25 mg.

N.B. The equivalent doses of Digitalis Leaf, Tincture, and Digoxin are 0·1 G., 1 ml., and 0·25 m.g. respectively.

Action

External. The glucosides are irritant and give rise to pain, burning, sneezing, coughing and inflammation. Digitoxin is much more irritant than digitalin.

Internal. *Gastro-intestinal tract.* Preparations of digitalis are somewhat irritating to the gastric mucosa partly owing to the glucosides, partly to the saponins.

Vomiting and diarrhœa are chiefly attributable to action on the central nervous system.

Heart. The frog's heart is affected by direct action on the muscle and conducting tissues only. There is reduction of conductivity with partial heart block; increased excitability, and increased contractility, with, therefore, augmented force of contraction of auricles and ventricle. After toxic doses the contractions are very irregular, and finally the ventricle is in frogs arrested in systole, firmly contracted, quite pale, and unable to respond to any stimuli.

In mammals the action is complicated by involvement of the nervous inhibitory mechanism in addition to direct action on the myocardium. This is brought about by stimulation of the carotid body by direct action of the drug. The impulses thus generated travel to the vagus centre *viâ* the vagus (depressor fibres) and give rise to impulses which return to the heart, through the vagus, and cause slowing of the beat. The view that digitalis had a direct effect on the vagus centre has been abandoned. This is the **first** or **therapeutic stage.** There is a longer diastolic pause. The ventricles, however, empty themselves more completely because of **increased contractility due to direct muscular action.** If the heart is already dilated, as is so often the case in disease, the muscular effect of digitalis predominates, and diastolic relaxation is diminished rather than increased. Flattening or inversion of the T-wave may be seen at this stage, and is due to action on the myocardium.

Digitalis also depresses the conductivity of the auriculo-ventricular bundle and thus causes a lengthening of the P-R interval in the electrocardiogram. This is partly due to reflex vagal action, but largely to direct effect on the muscular tissue of the bundle of His. Increased force of muscular contraction increases the refractory period and decreases the conduction rate.

In the **second tage, or stage of poisoning**, the inhibitory action predominates and the pulse is slow, *e.g.* 50–60 per minute. The total output of the heart is now reduced because **the slowing effect outweighs that of myocardial stimulation.** Heart-block is more pronounced. Extrasystoles with coupling of the heart-beat may arise owing to the increased irritability of the heart muscle. At this stage vomiting is common probably as a reflex effect of cardiac stimulation.

In the **third stage,** never seen clinically, the augmented irritability of the myocardium overcomes the vagal inhibitory action and the **heart rate rises quickly.** Heart-block may now be complete and is due to a combination of vagal inhibition and direct muscular action on the bundle of His. Irregularity due to auricular and ventricular extrasystoles culminates in ventricular fibrillation and death.

Vessels. In man, therapeutic doses of digitalis do not affect the vessels, but in animals large doses contract them by direct action. Improvement in the general circulation effected by digitalis results in lowering of the activity of the vaso-constrictor centre. The **blood pressure** is thus **unaffected.** This allows of increased capacity of the arterial bed. At the same time, owing to the more complete emptying of the heart at each systole and the longer diastolic pause, the abnormally high venous pressure falls to normal. It is unnecessary to postulate a specific digitalis dilator effect on the veins to account for the fall of intra-auricular pressure.

Kidney. In healthy men and animals digitalis produces slight diuresis, in patients with heart disease it is generally a powerful **diuretic.** It acts by improving the circulation of blood through the kidneys.

Temperature. Moderate doses reduce the temperature in fever from action on the thermotaxic centre.

Absorption and excretion. The glucosides are partly destroyed in the bowel, but that which survives is absorbed from the small intestine. Digitoxin, digoxin, and the tincture reach the blood stream fairly quickly, for their effect on the electrocardiogram is demonstrable in four hours. The full effect is attained in six hours and persists for a day. Digoxin is absorbed fairly completely from the alimentary canal, and a single dose of 0·0015 G. ($\frac{1}{40}$ gr.) is excreted in a week. Other preparations are absorbed more slowly.

The prolonged action of digitalis after absorption indicates the very real danger of cumulative action. Strophanthin is destroyed in a day, but half the principles of digitalis are still active after four days. Of practical importance is the fact that the average individual can completely destroy the equivalent of 7 to 10 minims of the official tincture administered thrice daily.

The skeletal muscles, liver and kidneys take up the bulk of the digitalis which is not consumed by the heart.

The small amount of the glucosides which is not destroyed in the tissues is excreted in urine and fæces.

Therapeutics

External. Digitalis is not used externally.

Internal. It is given in cases of cardiac disorder. The standardized tinctures and the pure substance digoxin are now the most popular preparations in use.

Auricular fibrillation: a condition in which the regular beats of the auricle are replaced by fibrillary twitching dependent upon circus movement in the auricle. The auriculo-ventricular bundle transmits these irregular impulses and the ventricular contraction and pulse are irregular, weak and rapid.

It is in auricular fibrillation that digitalis acts so well that it may be regarded as a specific, causing the ventricular contractions and hence the pulse to become slow, regular, and strong. But the auricle continues to fibrillate, the improvement being due to the action of digitalis, producing partial heart-block so that only a few of the numerous auricular impulses are allowed to pass regularly to the ventricle. The ventricle therefore gets a proper rest between each beat. The action is in part vagal and partly a direct one on the conducting tissues. The vagal action is quite the most important in therapeutic doses and can be abolished by the administration of $\frac{1}{30}$ gr. atropine.

Massive-dose treatment. In urgent cases of fibrillation the tincture should be given in a full dose to start with, *i.e.* 0·125 mil (♏ ii) per pound of body weight in a single dose on the first day when a full therapeutic result will be obtained in six to eight hours. If vomiting owing to congestive heart failure be present a similar result may be obtained by a single intravenous dose of $\frac{1}{33}$ gr. strophanthin, which acts in thirty minutes, or by tincture of digitalis 0·1 mil (♏ i ss) per pound of body weight per rectum. In the latter case a simple enema should be given six hours prior to the dose which is diluted with 3 oz. of normal saline. The full effect is obtained in about eight hours. Complete elimination of a massive dose of digitalis takes twelve to thirteen days ; a small maintenance dose is usually needed in twelve days. After strophanthin the interval is eight days.

The introduction of digoxin has made the massive-dose treatment with digitalis unnecessary. A dose of 1·5 mg. by mouth, or 1 mg. intravenously, should be given for an urgent case and followed by 0·25 mg. thrice daily afterwards.

Auricular flutter, in which the auricles beat rapidly but regularly and in which the ventricular rate is usually high, is converted into auricular fibrillation by digitalis. If the drug be then discontinued, the heart will resume its normal rhythm.

Apart from auricular flutter and fibrillation, the main indication for digitalis is **congestive heart failure** : it is pointless to give the drug in cases of well compensated valvular disease. It must be remembered that the coronary arteries fill during diastole. The prolongation of this phase by digitalis is, therefore, of direct benefit to the heart muscle. When œdema is present Guy's pill is of value. It consists of mercurial pill, digitalis leaves, and squill, a grain of each, made up with extract of henbane. The combined use of digitalis and mersalyl is more efficient and has supplanted it.

The increased force of the heart-beat produced by digitalis results in a lowering of venous pressure.

The sitting position adopted by a patient with cardiac failure likewise results in a fall of venous pressure with lowering of cardiac output and of the blood in the pulmonary circulation. This raises the vital capacity. At the same time the consequent reduction of anoxæmia lowers the activity of the vasomotor centre with ensuing vaso-dilatation. The renal arterioles take part in this and, therefore, the urinary secretion is increased. In the middle-aged hyperpietic exhibiting enlargement of the left ventricle, dyspnœa, and œdema of the ankles, digitalis is often of unquestionable value. High blood pressure is no contra-indication to its use.

Digitalis is useless in acute toxic myocarditis such as occurs in typhoid, pneumonia and many other fevers.

Digitalis is cumulative. Patients who have taken it for long will sometimes suddenly show symptoms of poisoning without any increase in the dose. This is because, as the drug is not destroyed and excreted as fast as it is absorbed, it accumulates in the body. The most important symptom of poisoning is slowing of the pulse, coupling of beats, and vomiting.

STROPHANTHUS

Strophanthus (B.P.). The dried ripe seeds of *Strophanthus kombé.*

Composition. It contains several glucosides, all derived from one aglucone, strophanthidin ($C_{23}H_{32}O_6$).

Preparation (B.P.)

Tinctura Strophanthi. Strophanthus; alcohol (70 per cent.). Standardized by biological assay.

Dose, 2—5 min. 0·12—0·3 ml.

Strophanthinum (B.P.C.). A mixture of glucosides obtained from strophanthus. It must possess 40 per cent. of the activity of anhydrous ouabain.

Characters. A white powder, moderately soluble in water.

Dose, $\frac{1}{240}$—$\frac{1}{60}$ gr. 0·25—1 mg.—by intramuscular or intravenous injection.

Action and Therapeutics

The action and uses of strophanthus are similar to those of digitalis. It has a more stimulant action on the myocardium. It acts more rapidly and is destroyed more quickly than the latter, and is thus of value in urgent cases of fibrillation for which a single dose is given intravenously. By the time that subsequent doses of digitalis start to act, strophanthin is largely eliminated. There is, therefore, no danger of serious summation of effect.

OUABAIN

Ouabainum (**B.P.**). *Synonym.* Strophanthin-G. A glucoside derived from *Strophanthus gratus.* It can be obtained in crystalline form.

Dose, $\frac{1}{500}$—$\frac{1}{240}$ gr. 0·12—0·25 mg.

Preparation (**B.P.**)

Injectio Ouabaini. Contains 0·25 mg. ($\frac{1}{240}$ gr.) in 1 ml. (15 min.).

Dose, $\frac{1}{500}$—$\frac{1}{240}$ gr. 0·12—0·25 mg.—by intravenous injection.

Action

After absorption the action is that of digitalis except that the fall of auricular pressure is much less marked and the stimulant action in the heart muscle is greater. It can be administered parenterally. Its absorption from the alimentary tract is often irregular and incomplete. It is pointless to use it for oral administration.

SQUILL

Scilla (**B.P.**). The bulb of *Urginea maritima.*

Composition. The chief constituents are—(1) *Scillitoxin* or scillin, a glucoside, the most active principle. (2) Scillipicrin also active, and closely related to scillitoxin.

Dose, 1—3 gr. 60—200 mg.

Preparations (**B.P.**)

1. **Acetum Scillæ.** *Synonym.* Vinegar of Squill. Squill, 10; dilute acetic acid, 100.

Dose, 10—30 min. 0·6—2 ml.

2. **Oxymel Scillæ.** Squill; acetic acid; purified honey; and water. Five per cent. of squill.

Dose, 30—60 min. 2—4 ml.

3. **Syrupus Scillæ.** Acetum Scillæ, 450; sugar; water, to 1000.

Dose, 30—60 min. 2—4 ml.

4. Tinctura Scillæ. Squill (10 per cent.)
Dose, 5—30 min. 0·3—2 ml.

Action

Squill so closely **resembles digitalis** in its action that the account of that drug will apply to squill with the following additions. Squill is a **more powerful gastro-intestinal irritant**; vomiting and purging may result from even moderate doses, but often this is not so. In the second place, some constituent of squill is excreted by the bronchial mucous membrane, and irritates it. The vascularity and the amount and fluidity of secretion are thereby increased. Squill is, therefore, an **expectorant.** Thirdly, squill in the course of its excretion through the kidneys stimulates them; it is, therefore, a **more energetic diuretic** than digitalis, and it may irritate the kidneys excessively.

Therapeutics

Because of its irritating properties squill is not given alone, but it is frequently combined with digitalis when that drug is administered for heart disease with œdema.

Squill is used as an expectorant, it is too irritating to the bronchial mucous membrane for it to be given in acute bronchitis; but it is valuable in chronic bronchitis if the secretion is scanty.

Squill should not be given in acute Bright's disease, for it is too irritating to the kidneys.

GROUP XXII

Emetics and Expectorants

Quillaia, Senega, Ipecacuanha, Emetine, Chiniofon

Drugs which are capable of exerting the above actions belong to such widely diverse groups that it is impossible to collect them for joint description in the sections which follow. Emesis and expectoration are produced by any substance which is sufficiently irritating to the gastric mucosa or, after absorption, to the vomiting centre in the medulla. Expectorant action occurs as a precursor of vomiting in association with many other symptoms, *e.g.* rapid pulse, pallor and sweating. Sub-emetic doses have been alleged to cause increased bronchial secretion without nausea or vomiting. This is probably quite untrue. The group of expectorants which act peripherally, *i.e.* on the bronchi, are in a totally different category, and their classification is dealt with at the end of this section.

Emetics. It is well known that the many complicated mechanisms involved in the act of vomiting are under the control of a centre in the medulla, which is capable of being stimulated by afferent impulses reaching it from many sources, such as the cerebrum, as when sights or smells cause sickness, the mouth, the pharynx, the œsophagus, the lungs, the heart, the stomach, the intestines, the biliary passages, the kidney, the peritoneum, and the uterus ; so that drugs acting on any of these organs, or on the centre itself, might be emetics. But it is usual, in describing drugs which cause vomiting, to mention only those that do so either by acting on the stomach or on the centre in the medulla, and they are divided into two corresponding classes. Those acting on the stomach are sometimes called **direct** emetics, because they act directly on this organ ; and those influencing the medulla are called **indirect** ; but some authors reserve the word direct for those acting on the medulla, and speak of those affecting the stomach as indirect. Considering this confusion, it is better to divide emetics into **local** and **central.**

The following is a list of those emetics which are commonly used.

(1) Apomorphine.
(2) Tartar emetic.
(3) Ipecacuanha.
(4) Alum.
(5) Ammonium carbonate.
(6) Copper sulphate.
(7) Zinc sulphate.
(8) Sodium chloride.
(9) Mustard.
(10) Warm water.

Of these apomorphine is the only one that acts solely centrally. The others all act chiefly on the stomach, but tartar emetic and ipecacuanha perhaps act partly centrally.

Therapeutics

Emetics have two uses. First, to remove the contents of the stomach, as in cases of poisoning. Secondly, emetics are used to expel the contents of the air-passages, especially in children, for they cannot expectorate well. For this purpose these drugs are given in full emetic doses to assist expulsion of secretion in, for instance, bronchitis. In choosing an emetic it will be remembered that although apomorphine, ipecacuanha, and tartar emetic are the most powerful they are the most depressant, and are therefore not suitable in many cases—such, for instance, as poisoning accompanied by severe collapse. When the poison is a powerful gastro-intestinal irritant, if the condition of the mouth and œsophagus will allow of it, it is preferable to wash out the stomach rather than to use an emetic.

Emetics are not permissible for patients suffering from aneurysm, hernia, prolapse of the uterus or rectum, peritonitis, or a tendency to hæmorrhage, because of the straining induced by the vomiting, which should make us cautious in giving them to those who have disease of their vessels or high tension in them, for the straining may lead to hæmorrhage.

Expectorants. These are drugs which aid the expulsion of the contents of the bronchial tubes. They are used in the treatment of bronchitis, bronchopneumonia, tracheitis and laryngitis. They are classified according to their point of action :

1. Reflex expectorants act by irritation of the stomach which stimulates the vomiting (possibly broncho-secretory) centre : the efferent path is formed by the secretory fibres of the vagus to the bronchial glands. Ipecacuanha, Antimony, Squill, Ammonium Carbonate, Grindelia, and Senega act in this way.

2. Central expectorants act by direct stimulation of the bronchial centre. Ipecacuanha and Grindelia possibly have some such action : Apomorphine entirely so.

3. Stimulants of secretory nerve-ends. Pilocarpine is an example of this type.

4. Stimulants of Bronchial Secretory Glands act when excreted through the bronchial mucosa. Iodides, Alkalies, Neutral salts, Creosote and certain volatile oils act at this point. Iodides have a specific effect apart from simple salt-action. Clinical investigations throw much doubt on the efficacy of reflex expectorants when used in therapeutic doses.

QUILLAIA BARK

Quillaia (B.P.). *Unoff. Synonyms.* Panama bark; Soap bark. The dried inner part of the bark of the tree *Quillaja saponaria.*

Composition. The chief constituent is saponin, a glucoside.

Preparation **(B.P.)**

Extractum Quillaiæ Liquidum. Quillaia in 45 per cent. alcohol.

SENEGA

Senega (B.P.). The dried root of *Polygala senega.* From North America.

Composition. The chief constituent is Senegin, a glucoside, identical with Saponin, found in Saponaria (Quillaia bark, *q.v.*), and many other plants.

Preparations **(B.P.)**

1. Extractum Senegæ Liquidum. Senega, dilute solution of ammonia and alcohol (60 per cent.).

Dose, 5—15 min. 0·3—1 ml.

2. Infusum Senegæ Concentratum. Senega, dilute solution of ammonia and alcohol (25 per cent.).

Dose, 30—60 min. 2—4 ml.

3. Infusum Senegæ.

Dose, ½—1 fl. oz. 15—30 ml.

4. Tinctura Senegæ. Liquid Extract of Senegæ, 2. Alcohol, 60 per cent., 8.

Dose, 30—60 min. 2—4 ml.

Action and Uses

That of a saponin. Occasionally used as an expectorant.

Saponins occur in many plants, but those derived from some plants are more poisonous than those derived from others. The more poisonous varieties are called sapotoxins. All saponins form a frothy solution in water. They are irritant to the alimentary mucosa and thus act as reflex expectorants.

The general action of sapotoxins and saponins is only seen after intravenous injection. It is characterized by vomiting, diarrhœa, subserous hæmorrhages and collapse. Hæmoglobinuria may be produced owing to the solvent action of saponin on lecithin. Cholesterin forms inactive compounds with these bodies.

Therapeutics

Quillaia was used as an **expectorant,** but in view of the irritative properties of its sapotoxins it has been superseded by less toxic drugs such as ipecacuanha.

Saponins are used to create a frothy foam for the production of **foam baths.** Air is forced through a warm saponin solution, and the resulting foam surrounds the patient's body, and acts as an insulating medium. Pyrexia and vaso-dilatation are produced with relief of pain and stiffness in such conditions as chronic arthritis.

IPECACUANHA

Ipecacuanha (B.P.). The dried root of *Cephaëlis ipecacuanha.* Brazil.

COMPOSITION. The chief constituents are alkaloids—(1) Emetine, $C_{28}H_{27}(CH_3)N_2O_4$. (2) Cephaeline, $C_{28}H_{38}N_2O_4$. (3) Psychotrine exists in minute quantities. Emetine is methylcephaeline. Cephaeline is a reduction product of psychotrine. All three are derivatives of isoquinoline. The action of emetine and cephaeline is similar; psychotrine is inert. Ipecacuanha contains also tannic acid and gums.

Ipecacuanha Præparata (B.P.). *Synonym.* Ipecacuanha Pulverata. Powdered ipecacuanha root contains 2 per cent, of the total alkaloids. The proportion of each varies in different specimens of the root, but as a rule there is twice as much emetine as cephaeline.

Dose, ½—2 gr. 30—120 mg.
15—30 gr. 1—2 G. (emetic).

Preparations (B.P.)

1. Extractum Ipecacuanhæ Liquidum. *Standardized to contain* 2·0 *per cent. of the alkaloids of the root.*

Dose, ½—2 min. 0·03—0·12 ml.
10—30 min. 0·6—2 ml. (emetic).

2. Pulvis Ipecacuanhæ et Opii. *Synonym.* Dover's powder *Strength:* 10 per cent. each of opium and ipecacuanha.
Dose, 5—10 gr. 0·3—0·6 G.

3. Tinctura Ipecacuanhæ. Contains 0·1 per cent. w/v of the total alkaloids calculated as emetine.

Dose, 10—30 min. 0·6—2 ml.
½—1 fl. oz. 15—30 ml. (emetic).

4. Trochiscus Morphinæ et Ipecacuanhæ. (*See* Morphine.)

EMETINE HYDROCHLORIDE

Emetinæ Hydrochloridum (**B.P.**)

SOURCE. The alkaloid from ipecacuanha root.

CHARACTERS. Colourless, crystalline powder: turns yellow on exposure. Freely soluble.

Dose, ½—1 gr. 30—60 mg.—by subcutaneous or intramuscular injection.

Preparation (**B.P.**)

Injectio Emetinæ Hydrochloridi. Contains 60 mg. (1 gr. in 1 ml. (15 min.).

Dose, ½—1 gr. 30—60 mg.

EMETINE-BISMUTH-IODIDE (E.B.I.)

Emetinæ et Bismuthi Iodidum (**B.P.**). A red powder containing 25 per cent. emetine. Insoluble in water.

Dose, 1—3 gr. 60—200 mg.—daily.

Iodoxyquinoline Derivatives Used in Amœbiasis

Chiniofonum (B.P.). *Synonym.* Pulvis Chiniofoni. *Unoff. Synonyms.* Yatren, Quinoxyl, Loretin.

SOURCE. A mixture of 7-iodo-8-hydroxyquinoline-5-sulphonic acid and sodium bicarbonate.

CHARACTERS. A pale yellow hygroscopic powder, containing 29 per cent. of iodine.

Dose, 1—8 gr. 60—500 mg.
15—75 gr. 1—5 G.—by rectal injection.

Vioform is iodochlorhydroxyquinoline. A slightly soluble greyish powder containing 40 per cent. of iodine.

Diodoquin is diiodohydroxyquinoline. It contains 64 per cent. of iodine. It is insoluble and seldom gives rise to signs of intestinal irritation.

Action

External. Ipecacuanha powder and emetine are powerful **irritants** to the skin, producing redness, vesication, and pustulation. Injected subcutaneously only slight irritant action is observed. Some individuals are very susceptible to the action of ipecacuanha, which in them may produce conjunctivitis, sneezing and bronchitis. The frequent handling of the powdered root may induce hypersensitivity so that finally the most minute quantities ingested or inhaled will precipitate an attack of asthma. Emetine has a special affinity for *Entamœba histolytica*, which it destroys in one part in five million in three days at a pH of 7·2. If the medium is not too acid it remains highly lethal even in such high dilution. It has been shown conclusively that amœbæ do not become emetine-resistant.

Internal. *Alimentary Canal.* Large doses are powerfully **emetic.** This is chiefly due to their irritant effect upon the stomach, but in a much less degree to the fact that emetine acts directly upon the vomiting centre in the medulla, as can be proved by observing that when the alkaloid is thrown directly into the circulation vomiting may follow before there is time for it to have been excreted into the stomach. Ipecacuanha is thus a powerful reflex and a weak central emetic. The irritant effect is continued in the intestine, and hyperæmia, excessive secretion, and purging result.

Circulation. Large or repeated doses of emetine cause degenerative changes in the myocardium with reduction of conductivity, fall of blood pressure, dyspnœa, and fainting.

Respiration. The respiration is affected only in so far as it is related to emesis. Sub-emetic doses act well as reflex expectorants.

Skin. Ipecacuanha is a mild **diaphoretic** in virtue of its emetic properties.

Muscles. Emetine causes degeneration of skeletal muscles with pain and paralysis.

Therapeutics

External. None.

Internal. Ipecacuanha is an excellent emetic and is used for this and for the associated expectorant effect.

It is a reflex expectorant and is employed in **acute bronchitis** when sputum is scanty and tenacious. In the dry cough of laryngitis and tracheitis, by producing an outpouring of secretions, it gives relief, especially if combined with opium, as in Dover's powder.

Emetine is a specific for **amœbic dysentery.** When ipecacuanha itself was used large doses were given—30 grs. (2 grms.) of the powdered root in a single dose on one day, 25 grs. the next, and so on till 145 grs. had been taken. This often made the patient sick.

Emetine hydrochloride, by deep subcutaneous or intramuscular injection, produces dramatic relief in acute amœbic dysentery and hepatitis. Daily injections of 1 gr. (0·06 grm.) are given for not more than twelve doses. The patient should be confined to bed or on very restricted activity because of the depressant effect of the drug on the myocardium. Acute hepatitis is often cured by this treatment alone. The dysenteric symptoms, though relieved, tend to recur in two-thirds of patients so treated, or they may be symptom-free yet harbouring the infection in the gut. In view of this fact combined drug treatment is now used as a routine. Amœbic abscess of the liver will usually disappear if treated by aspiration and a course of emetine injections.

Emetine bismuth iodide slowly liberates emetine in the intestine, and thus helps to eliminate amœbæ which have not been destroyed by the parenteral administration of the hydrochloride. It should be given as an uncompressed powder in gelatine capsules each containing 1 gr. As E.B.I. may produce vomiting it may be necessary to precede its administration by the giving of a sedative, *e.g.* Tr. opii minims 10 half-an-hour before. Three grains are given each evening for twelve days. It is claimed that 95 per cent. of carriers can be cured by this treatment alone.

Chiniofon, Vioform, and Diodoquin are iodine-oxyquinoline compounds which are used as adjuvants in the treatment of amœbiasis. It is probable that the liberation of iodine in the gut is responsible for the beneficial effect. Chiniofon *in vitro* has amœbicidal action in concentrations of 1 : 100. It may be given by mouth, 4 grs. four times daily for two weeks. It may cause diarrhœa. Given by mouth alone it fails to exterminate cysts. It may be administered by mouth and as a retention enema, daily for ten days, or, more commonly, only as an enema, whilst E.B.I. is given in the manner described. The bowel is cleansed with a 2 per cent. sodium bicarbonate enema soon after a light breakfast. Subsequently 2½ per cent. chiniofon in 7 ozs. warm water is run slowly into the rectum, the patient lying on the left with the buttocks raised. He then lies on his back for half an hour, then on his right side. The enema is retained for eight hours.

Vioform is given in gelatine capsules, 4 grs. thrice daily for ten days. It is too irritant for use as an enema. It is less effective than chiniofon.

Diodoquin is of undoubted value in chronic amœbic dysentery. Ten grains in tablet form are given thrice daily for twenty days. It is the least toxic of the three oxyquinoline compounds. It may be used in conjunction with emetine injections in hepatitis, or as a preliminary to E.B.I. and chiniofon in chronic dysentery.

The present day treatment of amœbiasis consists of six daily injections of emetine hydrochloride (1 gr. each) if dysenteric symptoms or hepatitis are present. Following this E.B.I. and chiniofon enemata for twelve days. Finally diodoquin by mouth as described above. Until the advent of this drug, after-treatment used to be carried out with pentalavent arsenicals by mouth, *e.g.* acetarsol or carbarsone grs. 4 twice daily for ten days.

Finally it should be noted that in severe, or resistant, amœbic dysentery the symptoms of the disease may be greatly aggravated by secondary bacterial invaders of the gut. Treatment with full doses of penicillin and succinyl sulphathiazole should then be instituted.

GROUP XXIII

Prussic Acid, Virginian Prune

HYDROCYANIC ACID

Acidum Hydrocyanicum Dilutum (B.P.C.). Dilute Prussic acid.

Source. Prepared by the interaction of potassium ferrocyanide and sulphuric acid. It is a 2 per cent. by weight solution of hydrogen cyanide, HCN.

Characters. A colourless, volatile, faintly acid liquid, having an almond-like odour. Very unstable.

Dose, 2—5 min. 0·12—0·3 ml.

Preparation **(B.P.C.)**

Tinctura Chloroformi et Morphinæ Composita. ½ ♏ of Acidum Hydrocyanicum Dilutum in 10 ♏, *i.e.* 5 per cent.

Dose, 5—15 min. 0·3—1 ml.

Hydrocyanic acid is contained in oil of bitter almonds. It is probably the active ingredient of the preparations of Virginian Prune.

Action

External. Hydrocyanic acid can pass through the epidermis, and then it paralyses the terminations of the sensory nerves; thus it is a **local anæsthetic and sedative.** It is very rapidly absorbed from raw surfaces, and causes poisoning if applied to them. A single drop of the pure acid placed inside the eye of even a moderately large animal will kill it instantly.

Internal. *Alimentary tract.* It is quickly absorbed by mucous membranes, and has the same anæsthetic and sedative effect on the mouth and stomach as on the skin.

Metabolism. Prussic acid and the cyanides so affect the protoplasm of the body tissues that the cells cannot take up oxygen from the blood in normal quantity. In consequence less CO_2 is formed and all the blood in the body is of a bright arterial tint. The condition of asphyxia which thus arises from inhibition of the internal respiratory exchange is actually brought about by paralysis of the intra-cellular ferments responsible for oxygen absorption. If blood be shaken up with prussic acid, oxyhæmoglobin is converted into cyanohæmatin, the oxygen being turned out. Prussic acid added to drawn blood prevents the usual effervescence of hydrogen peroxide with blood because it paralyses the peroxidase ferment. Neither of these actions is seen in life, for sufficient prussic acid to cause them would kill before they could take place. Lactic acid and sugar are found in the urine if much prussic acid has been taken. They are often present when oxidation of tissues is imperfect.

Heart. Large doses cause instantaneous **diastolic arrest.** As this is also true if the drug is applied locally, we may conclude that large doses paralyse the heart directly. A small dose will cause a slowing of the pulse from stimulation of the vagus centre, and the stoppage from larger doses is due both to the direct action on the heart and to that on the medulla.

Vaso-motor system. The vaso-motor centre in the medulla is first briefly stimulated, and the blood pressure rises, but soon it is profoundly **paralysed**; **blood pressure** therefore falls **very low.**

Respiration. The respiratory centre is at first powerfully stimulated, the respiratory excursions increasing in depth and frequency. This is followed by paralysis which rapidly supervenes after large doses.

Nervous system. Cerebrum. Medicinal doses of prussic acid have no effect on the cerebrum. Toxic doses cause deep insensibility and coma. In man convulsions are rarely seen ; in animals they are common. It is probable that the coma and convulsions are due to the direct effect on the brain, but they may in part be due to the altered circulation through it, or to the asphyxia.

Peripheral nerves and muscles. In animals dead of prussic acid poisoning these are unexcitable. This paralysing effect is due to a direct action on the nerves and muscles themselves, for it does not occur in the peripheral part of a limb if it is connected ith the rest of the body only by its nerve, for, as no blood is circulating through the distal part of the limb, no prussic acid reaches it ; but if the acid be applied locally to the severed limb, the nerve and muscles are paralysed. It will be noticed that it depresses all functions, indeed it is a powerful protoplasmic poison. The pupil is dilated.

Excretion. Prussic acid is rapidly changed to harmless sulphocyanides in the tissues and is excreted in the urine in this form.

Therapeutics

External. Lotions of about 10 ♏ (6 decimils) of the diluted acid to 1 fl. oz. (30 mils) of water are valuable for allaying itching due to any cause. If the skin is abraded they must not be used.

Internal. Small doses, 2 to 4 ♏ (12 to 25 centimils) of the diluted acid, are used for their sedative effect on the nerves of the stomach, to allay vomiting, and to relieve gastric pain, whatever may be their cause, and often with good effect. A useful way of giving it is in an effervescing draught. It is a common ingredient of cough mixtures, but any effect of medicinal doses on the respiratory centre would be in the nature of stimulation. It is therefore of no value unless cough is due to reflex irritation from the stomach.

Toxicology

With a large dose the symptoms usually begin in a few seconds ; it is rare for them to be delayed more than two minutes. The patient is perfectly insensible, the eyes are fixed and glistening, the pupils dilated, the limbs flaccid, the skin cold and clammy. The respiration is slow, deep, and convulsive ; the pulse is almost imperceptible.

Treatment consists of evacuation of the stomach and artificial respiration.

Virginian Prune Bark

Prunus Serotina (B.P.). The bark of *Prunus serotina*, the wild cherry, collected in the autumn.

Composition. It contains (1) Amygdalin, which yields with water glucose, hydrocyanic acid, and essential oil of bitter almonds (*q.v.*) (2) Emulsin.

Preparation (B.P.)

Syrupus Pruni Serotinæ. *Synonym.* Syrup of Wild Cherry. Virginian prune bark, 150; refined sugar; glycerin; water to 1000. Percolate.

Dose, 30—120 min. 2—8 ml.

Action and Therapeutics

It may be that the ease with which prussic acid can be derived from this drug explains its employment for cough. The *rationale* of this use has been referred to in discussing prussic acid. Virginian prune is a favourite remedy, and the syrup is a very useful flavouring agent for cough mixtures.

Thiocyanates (Sulphocyanates). The effects of the potassium and sodium salts are due to the linkage $-S-C\equiv N$. This does not dissociate and, therefore, the toxic action of HCN is not produced.

The thiocyanates have a nitrite-like action in relaxing smooth muscle. They are, therefore, used for the treatment of hypertension. They may also cause salivation, lachrymation, and various skin rashes.

The drug is excreted unchanged by the kidneys. It does not permeate tissue cells.

Toxic effects are muscular weakness, cramp, coryza, dermatitis goitre, vomiting, diarrhœa, severe fall of blood pressure, confusion, convulsions and death. These are likely to arise at serum levels above 15 mgm. per cent.

Therapeutics

Thiocyanates are used solely in the treatment of essential hypertension (hyperpiesia). A close watch must be kept on the concentration of the drug in the serum for renal excretion is apt to be erratic. Probably 10 mgm. per 100 c.c. should not be exceeded.

A fall of systolic and diastolic pressure results but is often not permanent. It is claimed that hypertensive headache is a special indication for thiocyanate administration.

The usual dose is 0·2 grm. thrice daily in water for 3 days; then once daily for 3 days. Subsequent dosage depends upon the serum-level reached. It may be 0·2 grm. on alternate days.

GROUP XXIV

Colchicum, Cinchophen

These drugs are used for gout

COLCHICUM

Colchici Cormus (B.P.). The fresh corm of *Colchicum autumnale* (meadow saffron), collected in the early summer.

Composition. The chief constituents are—(1) *Colchicine*, the active alkaloid. (2) Colchiceine which is less active.

Preparation (**B.P.**)

Extractum Colchici Siccum. Made from the corm by percolation with alcohol, evaporation of residue, and adjustment with lactose to contain 1 per cent. of colchicine.

Dose, $\frac{1}{6}$—$\frac{1}{2}$ gr. 10—30 mg.

Colchici Semen (B.P.). The dried ripe seeds of *Colchicum autumnale.*

Composition. The chief constituents are—(1) The same as of the corm, but the proportion of the active alkaloid colchicine is larger. (2) A volatile oil in addition.

Preparations (**B.P.**)

1. Extractum Colchici Liquidum. *Synonym.* Fluidextractum Colchici. Contains 0·3 per cent. of colchicine.

Dose (not official), **2—5 min. 0·12—0·3 ml.**

2. Tinctura Colchici. A mixture of liquid extract of colchicum, or of colchicum corm, and alcohol (60 per cent.). Contains 0·03 per cent. of colchicine.

Dose, 5—15 min. 0·3—1 ml.

Colchicina (B.P.). $C_{22}H_{25}O_6N$. Pale yellow, soluble, crystals.
Dose, $\frac{1}{120}$—$\frac{1}{60}$ gr. 0·5—1 mg.
Total Dose, $\frac{1}{30}$—$\frac{1}{8}$ gr. 2—8 mg.

Action

External. When applied to the skin colchicum acts as an irritant, causing hyperæmia and smarting, and the dust inhaled gives rise to sneezing.

Internal. *Gastro-intestinal tract.* In moderate medicinal doses colchicum produces no effect on most persons, but with others it causes loss of appetite, and a little **purging, nausea,** and **colic.** In larger doses it gives rise, in all persons, to great abdominal pain, vomiting, and profuse diarrhœa with the passage of blood. It is in fact a powerful **gastro-intestinal irritant.** There is also great prostration, the pulse becomes small, rapid, and thready, the skin cold and bedewed with sweat, and the respiration slow; death is due to collapse. It is probable that these results are the consequence of the severe gastro-enteritis. They are produced if colchicine is injected subcutaneously, a circumstance which indicates that this alkaloid is an active principle of colchicum, and that it is excreted into the intestine.

Kidneys. Colchicum may produce anuria, or oliguria and hæmaturia, after an initial diuresis. The same effect may be seen after the injection of colchicine. It is due to irritant action at the point of excretion and is comparable with the enteritis from the same cause. No increase of uric acid output is produced.

Blood. The first effect is to diminish the number of polymorphonuclear cells in the blood, but later there is a considerable increase.

Therapeutics

Colchicum is used for **gout.** Given during the attack, it most markedly relieves the pain. It is useless as a prophylactic. It is a true specific ; how it acts is not known. If any symptoms of gastric or intestinal irritation appear, its use must be discontinued for a time. Colchicine may be given intravenously in acute cases or by mouth two-hourly for eight doses. It is too irritant for hypodermic injection.

CINCHOPHEN

Cinchophenum (B.P.). *Synonym.* Quinophan. *Tr. Names.* Atophan, Agotan.

CHARACTERS. A yellowish, insoluble, amorphous powder.

COMPOSITION. Phenylquinoline carboxylic acid.

Dose, 5—10 gr. 0·3—0·6 G.—best given thrice daily for two consecutive days in eight.

Action

A single dose of cinchophen causes an increase of uric acid excretion in the urine which deposits urates on standing. The output is augmented by 50 to 300 per cent. There is a coincident fall of blood uric acid. This effect is not produced by repeated doses ; in fact after the first day the uric acid output rapidly approaches the normal, and may even fall below it. On the other hand, there may be a persistently high output, though never so great as that following the initial dose. This is due to an increased formation of uric acid in the tissues.

The action of cinchophen is exerted on the kidneys either rendering them more permeable to uric acid, or preventing the normal reabsorption of urates from the tubules.

Cinchophen shares with other aromatic substances the property of reducing pyrexia and relieving pain. It is a stomach irritant and will produce peptic ulcers in animals.

Prolonged administration, particularly to susceptible individuals, leads to various skin rashes, including purpura, palpitation, fall of blood pressure, cyanosis, anorexia, vomiting, epigastric pain, fever, jaundice, necrosis of the liver, and death in cholæmic coma.

All these symptoms do not necessarily occur in any one individual.

Neocinchophen or Novatophan is an ester of methylcinchophen. Its action is that of cinchophen, but it is tasteless, non-irritating and less likely to damage the liver.

Therapeutics

Cinchophen is used solely for **gout.** It scarcely affects the acute attack, but is valuable in its prevention and in chronic gout. It is pointless and dangerous to take it continuously.

GROUP XXV

Vegetable Drugs acting on the Uterus

Ergot, Ergotoxine, Ergotamine, Ergometrine, Histamine

ERGOT

Ergot is no part of the rye grain, which completely disappears as the ergot develops.

Composition. The chief constituents are—(1) *Ergotoxine*, an amorphous alkaloid forming a crystalline phosphate. (2) *Ergotinine* is the anhydride of ergotoxine. (3) *Ergometrine.* (4) *Ergotamine.* (5) *Tyramine* or parahydroxyphenylethylamine. This has a powerful physiological action resembling that of adrenaline. It may also be obtained from putrid meat and from tyrosine by loss of CO_2 caused by bacteria. (6) *Histamine*, which is formed from histidine by bacterial removal of CO_2 and is present in extracts of intestinal mucous membrane. (7) Fixed oil, 30 per cent. (8) Trimethylamine, causing the odour. (9) Tannin. (10) Saponin.

Ergota (B.P.). *Synonym.* Secale cornutum I. A. Contains not less than 0 2 per cent. of the total alkaloids.

Preparations (B.P.)

1. **Ergota Præparata (B.P.).** Prepared ergot is powdered ergot deprived of its fat in order to preserve the alkaloid content. It contains 0·2 per cent. of total alkaloids.

Dose, $2\frac{1}{2}$—8 gr. 0·15—0·5 G.

2. **Extractum Ergotæ Liquidum.** Ergot; tartaric acid and alcohol (50 per cent.).

Dose, 10—20 min. 0·6—1·2 ml.

3. **Tabellæ Ergotæ Præparatæ.** Contain $2\frac{1}{2}$ gr.—0·15 G. in each.

Ergotaminæ Tartras (B.P.). *Tr. Name.* Femergin.

Dose, $\frac{1}{60}$—$\frac{1}{30}$ gr. 1—2 mg.
$\frac{1}{240}$—$\frac{1}{120}$ **gr. 0·25—0·5 mg.**—by injection.

Ergometrina (B.P.C.). $C_{19}H_{23}O_2N_3$. Ergometrine.

SOURCE. An alkaloid obtained from ergot by crystallization from chloroform.

CHARACTERS. Colourless crystals which are oxidized slowly on exposure to air and turn brown. Soluble in alcohol and dilute acids: moderately soluble in water. Resistant to boiling.

Dose, $\frac{1}{120}$—$\frac{1}{60}$ gr. 0·5—1 mg.
$\frac{1}{240}$—$\frac{1}{120}$ **gr. 0·25—0·5 mg.**—by intramuscular injection.
$\frac{1}{480}$—$\frac{1}{240}$ **gr. 0·125—0·25 mg.**—by intravenous injection.

Ergometrinæ Maleas (B.P.). *Synonym.* Ergonovine Maleate. Soluble in 36 parts of water.

Dose, $\frac{1}{120}$—$\frac{1}{60}$ gr. 0·5—1 mg.
$\frac{1}{240}$—$\frac{1}{120}$ **gr. 0·25—0·5 mg.**—by intramuscular injection.
$\frac{1}{480}$—$\frac{1}{240}$ **gr. 0·125—0·25 mg.**—by intravenous injection.

Preparation (B.P.)

Injectio Ergometrinæ Maleatis.

Dose. As above for injection. Contains $\frac{1}{120}$ **gr. in 15 min.** 0·5 mg. in 1 ml.

Action

The action of ergot was for many years attributed to the effect of two of its constituents, viz., ergotoxine and ergotamine, which produce the same pharmacological action both qualitatively and quantitatively. Histamine, which is probably not a true constituent of ergot though often present as an impurity, produces no action when given by mouth ; it will be considered separately at the end of this chapter. Whereas ergotoxine and ergotamine produce no demonstrable effect on the organism for half an hour or more after administration by mouth, yet the liquid extract of ergot (**B.P.** 1914 and 1932) causes pronounced contractions of the uterus within ten minutes of its being taken. As the 1914 extract of ergot could contain only very little ergotoxine or ergotamine because of their slight solubility in water it was clear that some other undiscovered constituent must be responsible for its unquestionable efficacy.

This problem, the existence of which was first appreciated by Moir, has been solved in the first place by clinical study which gave rise later to further chemical investigations of ergot. The result is the discovery of a new and all-important alkaloid, ergometrine. The following account of the action of ergot must therefore be regarded as one of the combined effect of ergotoxine, ergotamine and ergometrine. Subsequently the manner in which ergometrine differs from the first two alkaloids will be made clear.

External. None.

Internal. The main action of ergot can be attributed to its stimulant action on plain muscle and paralysis of the motor sympathetic nerves.

Cardio-vascular system. Ergot preparations if injected give rise to a considerable rise of blood pressure due to contraction of arteries and arterioles, especially in the splanchnic area. The action is due to stimulation of the vaso-constrictor terminations in the vessel wall. Large doses paralyse them. In that case subsequent injection of adrenaline causes a fall of blood-pressure from stimulation of vaso-dilator nerve endings, an effect which is usually masked by the stronger action on constrictors. The heart rate rises at first, but soon becomes slow owing to stimulation of the vagus centre by the high blood pressure. The initial rise in heart rate is due to stimulation of the accelerator terminations.

Alimentary system. Unaffected.

Respiratory system. The respiration rate is considerably raised by poisonous doses due to direct stimulation of the medullary centre.

The pupil is greatly constricted when ergot is injected intravenously. Atropine does not abolish this effect, which must, therefore, be produced at a point distal to the nerve termination.

Uterus. In therapeutic doses the only effect which ergot exerts is on the uterus. This is most marked during and for a few days after labour when it tends to produce spasm. In large doses the contractions may follow so closely one upon the other that there is no time for adequate relaxation between; the state is then virtually one of tonic contraction. With smaller doses powerful contractions are followed by more complete relaxations, the effect persisting for one or two hours. The response of the non-pregnant uterus is variable and slight.

Comparison of the action of ergotoxine and ergotamine on the one hand and ergometrine on the other. The effects of these substances were studied on the human uterus on the seventh day of the puerperium. A rubber bag connected by a water-filled tube to a manometer was inserted into the uterus, whose contractions could thus be recorded. The results were as follows :—

1. The ergotoxine-ergotamine group (hereinafter referred to as E-E), which includes the more recently isolated alkaloids sensibamine and ergoclavine, in 3 mg. doses produces erratic and relatively feeble contractions of the uterus in thirty minutes or more when administered by mouth. The official liquid extract (which also contains ergometrine) causes a sudden onset of rapid contractions in five to ten minutes when given in therapeutic doses. The contractions are very rapid during the first hour, after which a second stage is entered upon during which they are spaced over longer intervals with intervening relaxation. This stage lasts one to two hours.

2. Ergometrine administered in 0·5 to 1 mg. doses by mouth causes contractions like those produced by the liquid extract in eight minutes.

3. The ergometrine effect is produced by 0·25 to 0·5 mg. intramuscularly in four minutes.

The E-E effect is thus produced in twenty minutes.

4. Ergometrine acts in eighty seconds if administered intravenously in doses of 0·05 to 0·1 mg. The E-E group in comparison act in six minutes.

5. Ergometrine causes no unpleasant constitutional reaction, and has but little if any effect on the blood pressure. The E-E group often causes headache, nausea and rise of blood pressure.

6. Owing to the absence of effect on the peripheral blood-vessels ergometrine will not cause gangrene. Its action is probably a direct one on uterine muscle. Large doses produce central nervous stimulation with tremors, convulsions, mydriasis, wide palpebral fissures, and tachycardia.

From these considerations it appears that ergometrine is therapeutically the most important constituent of ergot, and will no doubt be estimated for standardization of the crude drug in the future.

Crude preparations of ergot may give rise to unexpected effects on the cardio-vascular system owing to the presence of histamine (iminazolylethylamine), and sometimes of acetylcholine. These effects are seen only after intravenous injection. The commonest is a profound fall of blood pressure due to histamine, which may be preceded by a transient rise due to ergotoxine. Slowing of the heart and prolongation of diastole may be due to acetylcholine.

As both substances are destroyed in the intestine they can have no effect if present in preparations administered by mouth.

Ergotism. If ergot be taken for a long time, the contraction of the arterioles, together with the associated thickening of their walls and intravascular clotting, leads to **gangrene** of various parts of the body, and this was a prominent symptom of ergotism (chronic poisoning by ergot) which used to be seen in the very poor, especially in Russia, who could get no better food than rye infested with *Claviceps purpurea.* The gangrene usually affects the fingers and toes only, but may involve an entire limb which finally separates at the line of demarcation and falls off without hæmorrhage. Local or massive gangrene of the internal organs, *e.g.* stomach, lung, uterus, have been reported, and cataract frequently develops in the lens of the eye. In the past ergotism accounted for many apparent cases of thromboangeitis obliterans.

Nervous system. A second variety of chronic ergotism affected the nervous system. The sufferer first complained of itching and tingling, and a sensation of insects running over the skin ; this was followed by **numbness** and **local anæsthesia.** These symptoms first appeared in the hands and feet, but spread over the whole body. They were followed by **tonic contractions** of various muscles, especially those of the extremities. The muscular power was lessened, and the gait was staggering. **Dimness of vision,** loss of hearing, and epileptiform convulsions were sometimes present. This variety of ergotism was usually accompanied by vomiting and diarrhœa. Death occurred from asphyxia, due to spasm and weakness of the respiratory muscles. The fact that there are two such distinct varieties of ergotism suggests that the latter type which was the least common was complicated by starvation and avitaminosis.

Enormous single doses of ergot appear to paralyse the vaso-motor centres, as well as the vaso-motor terminations, and then the blood pressure falls from vascular dilatation and cardiac depression.

Therapeutics

The liquid extract of ergot, or ergometrine, is used almost exclusively for action on the uterus immediately after child-birth. By promoting a prompt and firm contraction of the womb the risk of post-partum hæmorrhage is greatly lessened.

It is unwise to use these preparations during labour because, as we have noted, the first stage of action is that of rapid contractions with incomplete relaxation. The fœtus would not thus be expelled, but probably killed. Rupture of the uterus might also occur. If inertia of the uterus develops when the fœtal head has reached the perineum the use of ergot may be permissible, however. Nowadays the oxytocic principle of pituitary gland is more often employed.

Ergometrine may also be used during Cæsarean section and should be injected as soon as the uterus is exposed. If labour has not yet started, however, its effect will be less certain than that of pituitrin.

Its use has also been advised for menorrhagia in the absence of organic disease. Usually, however, this symptom is due to a disturbance of the anterior pituitary-ovarian balance, and appropriate endocrine preparations are likely to replace ergot in this connection.

Ergotoxine will in future be used later in the puerperium if involution of the uterus is delayed. It will excite rhythmical contractions and assist in the expulsion of any retained products without causing violent uterine spasm.

The use of ergot preparations in the treatment of internal hæmorrhage is now a matter of historical interest only. Given by mouth, the vascular system would be unaffected by them, and if injected the rise of blood pressure produced would be as likely to aggravate the hæmorrhage as the arteriolar contraction would be to arrest it.

Ergotamine in the form of the tartrate (Femergin) has been used as a form of treatment of **migraine.** 0·25 mg. intravenously, 0·5 mg. subcutaneously or 1 mg. by mouth are the suggested doses. Vomiting, rise of blood pressure and bradycardia follow the injection. The vomiting is central in origin, and stimulation of the medullary centres is probably the only way in which ergotamine differs from ergotoxine in action. It is claimed that headache is relieved according to the method of administration in half, one, and two hours respectively. Oral administration is uncertain in its effect, however.

These happy results are by no means invariably achieved and occasionally the vaso-motor reactions are excessively unpleasant. Cramp in the legs may last for twenty-four hours after a therapeutic injection. It can be overcome by the administration of calcium gluconate intravenously. Vomiting can be prevented by giving $\frac{1}{100}$ gr. atropine.

The mode of action of ergotamine in migraine cannot be explained until the precise changes responsible for the headache are determined. The beneficial effect is independent of any action on the sympathetic, for it was exhibited regularly in a patient who had already been subjected to bilateral cervical sympathectomy.

Bellergal, which consists of a combination of ergotamine, lævohyoscyamine and phenobarbitone, is often of great value in the relief of migraine. It is possible that hyoscyamine acts by inducing relaxation of cerebral arteries in a state of spasm. In any case its presence would be valuable by blocking the vagal impulses set up by ergotamine which cause vomiting.

HISTAMINE

SOURCE. An amine derived from histidine and occurring naturally in the presence of putrefying protein, and in the intestine.

Histaminæ Phosphas Acidus (B.P.). *Synonym.* Histaminæ Phosphas. $C_5H_9N_3,2H_3PO_4$.

SOURCE. Action of phosphoric acid on histamine.

CHARACTERS. Colourless crystals. *Solubility:* 1 in 4·5 water. Sterilize in an autoclave, not by boiling.

Dose, $\frac{1}{120}$—$\frac{1}{60}$ gr. 0·5—1 mg.—by subcutaneous injection.

Preparation **(B.P.)**

Injectio Histaminæ Phosphatis Acidi. Contains 1 mg. ($\frac{1}{60}$ gr.) in 1 ml. (15 min.).

Dose, $\frac{1}{120}$—$\frac{1}{60}$ gr. 0·5—1 mg.

Action

Histamine is destroyed in the alimentary tract. When injected intravenously or subcutaneously, it powerfully stimulates unstriped muscle by direct action. This may cause uterine and bronchiolar spasm. The muscle of the alimentary tract is affected to a small extent, causing contractions of stomach and intestine. The salivary, gastric, lachrymal, pancreatic and intestinal glands are stimulated to secrete profusely. This effect is due to stimulation of the terminations of the post-ganglionic parasympathetic fibres. It is antagonized by atropine.

The most important effect is exerted upon the circulation. At the point of injection temporary pallor is replaced by a red flare, in the centre of which a wheal develops. After absorption a profound fall of blood pressure occurs as in secondary shock. This is due to widespread capillary dilatation associated with arteriolar contraction. The victim thus bleeds himself into his splanchnic vessels. Probably histamine, or a similar substance, is produced by tissue injury and is directly responsible for the phenomena of shock. Likewise it is probably the immediate cause of anaphylaxis and many allergic manifestations.

Therapeutic doses cause flushing of the skin, headache and tachycardia.

Therapeutics

Histamine is used as a **test of gastric secretory activity.** Thus in true achylia, as found in pernicious anæmia, its injection causes no secretory response. In achlorhydria due to chronic gastritis free hydrochloric acid may be found in the stomach after the injection of 0·3 to 0·5 mg. of the phosphate.

Histamine has also been used as histamine acid phosphate, 1 mg. in 1 c.c., for cases of **rheumatoid arthritis** with faulty skin circulation, **fibrositis** and chilblain. 0·1 to 0·5 mg. is given thrice weekly.

Benadryl, Antistine, Anthisan

Anti-histamine Preparations. Certain trade preparations are available for the treatment of those diseases probably associated with the liberation of histamine, viz., urticaria and hay-fever. They can be shown experimentally to possess remarkable antihistamine properties. Thus they antagonize the effect of histamine on intestinal muscles in much lower concentration than that needed to counteract the effect of acetylcholine and barium. In short they have a specificity of action against histamine. They tend to reduce gastric acidity, but action here is less reliable. The fall of blood pressure from histamine is partially relieved by them.

Uses

The main therapeutic indications are **urticaria,** spasmodic **rhinorrhœa,** and **hay-fever.** Their efficacy in asthma and gastric hyperacidity is doubtful. They are said to be of value in **erythema multiforme** and **enterospasm.** They may produce nausea and drowsiness. Drowsiness can be prevented by the simultaneous administration of ephedrine.

Morphine and soporifics should not be given concurrently with them.

The preparations named above differ widely in chemical construction. As their use is still in an experimental stage the dosage should be that recommended on the label.

GROUP XXVI

The Heavy Metals

Lead, Silver, Gold, Zinc, Copper, Manganese, Aluminium, Iron, Mercury, Thallium, Radium and Thorium

The heavy metals produce pharmacological effects only when dissociated into ions of the metal or of an oxide.

Their local action is due to the precipitation of proteins to which they become intimately adsorbed. The astringent effect increases with the dissociability of the salt and the actual metal of its composition, *e.g.* lead, is highly astringent, mercury only slightly so. An irritant action is also seen and is chiefly referable to the acid radicle of the salt; thus the chlorides are more corrosive than the acetates. Weak solutions of metallic salts produce a protective pellicle by their astringent action: stronger solutions redissolve the precipitate, penetrate further into the tissues and cause much inflammatory reaction. It will be seen, therefore, that the action of the group is a mixture of astringent and corrosive effects, the predominance of one over the other being determined by the various factors cited.

Absorption is slow and excretion even more tardy, so that there is a pronounced tendency towards cumulative action. The route of excretion is chiefly through the alimentary tract, particularly in the saliva and through the colonic mucosa, which may be greatly irritated in the process. The heavy metals are widely distributed throughout the organs of the body, but the bulk of the majority is to be found in the liver.

Dilute solutions exert a marked antiseptic action, *e.g.* 1 part in 1 million of copper sulphate kills *B. typhosus* in two hours if suspended in distilled water: the presence of organic matter rapidly diminishes their activity, but the power of preventing microbial growth is much stronger than that of destruction of the organisms.

The general action of the heavy metals is exerted chiefly on the brain, nerves, alimentary tract and kidneys. It will be discussed in detail in connection with the individual members of the group.

LEAD

Plumbum.

1. Plumbi Monoxidum (B.P.). PbO. *Synonym.* Lead oxide.
Source. Oxidation of molten lead.

Characters. Pale brick-red heavy scales. Insoluble in water, soluble in nitric and acetic acids.

2. Plumbi Acetas (B.P.). Lead Acetate. $Pb(C_2H_3O_2)_2 3H_2O$. *Synonym.* Sugar of lead.

Characters. White prisms, slightly efflorescent and of a sweet taste. *Solubility:* 10 in 25 of water.

Dose, ½—2 gr. 30—120 mg.

Preparations (B.P.)

1. Liquor Plumbi Subacetatis Fortis. Strong solution of lead subacetate. *Unoff. Synonym.* Goulard's extract. Lead acetate; lead oxide; water. *Strength:* 25 per cent. of the subacetate.

2. Liquor Plumbi Subacetatis Dilutus. *Unoff. Synonyms.* Goulard water, Goulard's lotion. Liquor Plumbi Subacetatis Fortis, 12·5; water, 1000.

Action

External. The action of lead salts on the unbroken skin is very slight; but when applied to the abraded skin, to sores and to ulcers, they coagulate the albumen of the discharge, thus forming a protective coat; they coagulate the albumen in the tissues themselves; and they directly, not reflexly, contract the small vessels; for these three reasons they are **powerfully astringent.** Any salt may be irritant and caustic if enough is used and it is sufficiently concentrated.

Internal. Lead salts act on mucous membranes as on the broken skin, and are powerfully astringent to all parts of the alimentary canal, from the mouth downwards. They thus produce constipation. Lead excites tonic contractions of unstriped muscle, hence the colic and abortion caused by it. It exerts a paralytic action on voluntary muscle especially if it is exercised. A concentration of lead which will cause rapid fatigue of an electrically stimulated muscle will have no effect upon the conductivity of the nerve. In lead poisoning it is usually the muscles which are used the most that are paralysed. It seems that this is not due to a neuritis, but to a lead myopathy. The explanation is that lead is in the blood as a relatively insoluble phosphate. This is converted into the more toxic lead lactate by the lactic acid produced in an active muscle. The metal is stored chiefly in the bones and may remain there for months or years as a potential source of intoxication should conditions favour a sudden withdrawal into the blood stream. (For other actions *see* Toxicology.)

Therapeutics

External. Lead salts are applied as lotions or ointments in many conditions for which an astringent, sedative effect is desired, as in eczema and ulceration. Their sedative effect is well seen in their use in pruritus. The Liquor Plumbi Subacetatis Fortis is rarely used, as it is strong enough to irritate ; the dilute form is that usually employed as a lotion.

Internal. Lead is occasionally used as an astringent in cases of diarrhœa, and the suppositories may be employed for rectal hæmorrhage. The subacetate of lead may be used as a gargle, or painted on as the glycerinum when an astringent effect on the mouth or pharynx is desired.

Lead causes abortion and is said to have a specific action on the syncytial cells of the chorionic villi which resemble those of malignant growths.

Toxicology

ACUTE LEAD POISONING. As when applied externally, so when taken internally, the salts of lead, if concentrated, are powerful irritants. Cases of acute poisoning are rare. The acetate is most frequently taken. There is a burning, sweetish taste in the mouth, thirst, vomiting, abdominal colic, and usually constipation, but if the bowels are open the fæces are black; the skin is cold, and there is collapse. If the patient live long enough, cramps in the legs, giddiness, torpor, coma, and convulsions are present. The symptoms of acute poisoning are entirely due to the local irritant effect and not the result of any action after absorption. If acute poisoning be recovered from, signs of chronic poisoning may then arise. *Post mortem.* The stomach and intestines show signs of irritant poisoning.

Treatment. Give emetics or wash out the stomach. Give sodium or magnesium sulphate to form an insoluble sulphate, and to open the bowels. If collapse is present, stimulants and warmth should be used.

CHRONIC LEAD POISONING. This is fully described in text-books on medicine. Among those who work in lead, it usually occurs because the dust in the air they breathe contains minute particles of lead compounds; formerly it was thought that they generally were taken into the body with food because the workers did not wash their hands before meals. Those who work at white-lead factories are very liable to it. It has also occurred in many ways from the impregnation of food and water with lead, especially from the storage of soft water in leaden cisterns and pipes.

Symptoms. The earliest are constipation and intestinal colic. After absorption it produces anæmia and punctate basophilia; it checks the separation of urates from the blood and their excretion by the kidneys, hence gout is very common in those poisoned by lead. As it circulates in the gums, and the lead-impregnated plasma bathes their epithelium, through which some of the sulphur in the food and in the tartar of the teeth has diffused, a lead sulphide is precipitated in the gums, and forms the well-known very dark blue line at the base of the teeth. For the same reason a blue line may occasionally be seen round the anus, and, after death, deposits of pigment in the intestines. Lead often appears to produce inflammation of the peripheral nerves, especially those supplying the extensors of the hand, and hence wrist-drop is a common symptom; but any muscles, and sometimes almost all the muscles of the body, may be paralysed from neuritis. It is noteworthy that the supinator longus usually escapes. Although it is probable that some neuritis is produced by the metal, the action on the muscle described earlier is probably the more important. The sensory fibres of the nerves are not often affected, hence pain and anæsthesia are rare; but pains, especially round the joints, may occur. In exceptional cases the anterior cornua of the spinal cord waste, and lead often affects the brain, causing saturnine lunacy, and also convulsions, known as saturnine epilepsy. Inflammation of the optic nerve, or optic neuritis, sometimes occurs, leading to blindness, which, however, may be present without any change in the nerve. Chronic interstitial nephritis also arises. The treatment consists chiefly in avoidance of the source of poisoning. Ammonium chloride and parathormone cause rapid withdrawal of lead from the bones and may even give rise to acute intoxication. This can be checked by giving calcium gluconate and alkalies. Very little lead passes out by the urine ; most leaves the body by the fæces.

Pregnant women suffering from lead poisoning commonly abort, and the drug has been frequently used as an abortifacient.

SILVER

Argentum

1. Argenti Nitras (B.P.). Silver Nitrate. $AgNO_3$ *Unoff. Synonym.* Lunar caustic.

CHARACTERS. Colourless, rhombic crystals. *Solubility*. 2 in 1 of water. Should be kept in the dark, as light blackens it.

2. Argenti Nitras Induratus (B.P.). *Synonym.* Toughened caustic.

SOURCE. Fuse together silver nitrate, 19 parts, and potassium nitrate, 1 part.

CHARACTERS. White or greyish-white cylindrical rods or cones. Freely soluble in water.

3. Argentoproteinum (B.P.). Silver Protein. *Synonyms.* Argentum-Proteinicum Forte ; Strong Protein Silver ; Silver Proteinate. *Tr. Name.* Protargol.

SOURCE. Prepared by the action of a silver compound on gelatin in the presence of alkali.

CHARACTERS. Brown, hygroscopic powder containing 8 per cent. of Ag.

Action

External. The action of silver salts is like that of lead salts, but is more powerful. Thus silver nitrate is a **caustic**, but it does not act deeply ; it is consequently an admirable agent for limited caustic action. Solutions are **astringents,** but they are more irritating than lead and cause pain. Silver salts, like lead salts, are **hæmostatic,** acting in precisely the same way. Weak solutions of the nitrate stimulate to healthier action indolent ulcers and other inflamed surfaces. The precipitate produced by the action of silver nitrate turns black when exposed to light. Silver proteinate is much less irritating than the inorganic salts, but also less germicidal.

Internal. Silver salts, when locally applied to the mucous membrane of the mouth, act as on the abraded skin. Silver is absorbed from the alimentary tract, for its long-continued use leads to a permanent, dark, bluish slate-colour first of the lips, inside of the cheeks, gums, nostrils, and eyelids, and later of the skin (argyria). This colour is due to the deposition of minute granules of metallic silver in the corium. Argyria has arisen of late in the makers of artificial pearls, and after the prolonged use of silver proteinate in the nose. In acute poisoning severe vomiting and nervous symptoms, as convulsions, are met with; the chronic form, seen often when silver was prescribed internally for nervous diseases, is shown by paralysis like that due to lead, albuminuria, and argyria. Some is passed in the fæces as the sulphide; some is deposited in the internal organs, especially the kidney.

Therapeutics

External. Nitrate of silver is used because it is from its limited action one of the best caustics, and may be employed to destroy warts and exuberant granulations, or to apply to bites; but it must be remembered that it is of no use when an extensive or deep action is required. A urethral bougie should contain ¼ gr. (16 milligrms.). Weak solutions (0·5 per cent.) are employed for granular lids and various forms of ophthalmia. One per cent. solutions are used for instillation into the conjunctival sac of the new-born as a prophylactic against gonorrhœal infection. Solutions of the nitrate will sometimes relieve pruritus, and may be applied to the red skin of a threatening bedsore. **Silver proteinate** is used as an antiseptic in ophthalmic work in 2 to 5 per cent. solutions, in the nose and throat in 5 to 10 per cent. solutions, and in the urethra in 1 to 2 per cent., and also as an injection for gonorrhœa. **Argyrol** is another silver proteinate containing 20 to 25 per cent. of silver. All these protein compounds dissociate slowly and therefore exert a weak action over a long period. They are used extensively in ophthalmic practice. **Collargol** (Colloid silver) being opaque to X-rays is in 20 per cent. solution injected into the ureter and renal pelvis for diagnostic purposes.

Internal. Silver salts are not much used internally, and their continuous employment is objectionable on account of the argyria produced. In concentrated form the nitrate may be applied to deaden pain arising from gum recession and exposure of the sensitive dental neck. The sensory nerve filaments are destroyed.

GOLD

Aurum. Atomic weight, 197·2

Auri et Sodii Thiosulphas (B.P.C.). Sodium Aurothiosulphate. $Na_3Au(S_2O_3)_2,2H_2O$.

Tr. Names. Sanocrysin, Crisalbine.

CHARACTERS. White soluble crystals containing 37 per cent. of gold.

Dose, 0·025 G. increased to 1·0 G. in 10 c.c. water, intravenously.

Action and Therapeutics

This salt of gold was believed to penetrate the lipoid covering of the tubercle bacillus and kill it, consequently it has been largely used for phthisis. The present view is that any beneficial effect is due to the reaction in the tissues of the host set up by the introduction of the metal. It produces a local reaction around the tuberculous lesion and often a general reaction as shown by pyrexia, rashes, albuminuria, diarrhœa, vomiting, neuritis, œdema of eyelids and eosinophilia. It was recommended in those cases of **tuberculosis** when collapse therapy had failed; when the disease was advancing in one lung, the other having been collapsed; early bilateral cases not responding to general measures, and in chronic pulmonary tuberculosis with good fibrotic reaction, but where the sputum was copious and rich in tubercle bacilli. Former enthusiasm for the drug has waned of recent years. An active tuberculous lesion may be irremediably aggravated by this drug. It was given twice or thrice weekly, *e.g.* 0·05 G. to 0·1 G. until 3 G. had been administered. It has also been used with success in the treatment of **lupus erythematosus.**

Sodii Aurothiomalas (B.P.). Contains 45 per cent. Au. *Tr. Name.* Myocrisin.

Dose, $\frac{1}{6}$ gr. increasing to $1\frac{1}{2}$ gr.—10 mg. increasing to 100 mg.—intramuscularly weekly.

Preparation (**B.P.**)

Injectio Sodii Aurothiomalatis. Aqueous solution containing 10 mg. ($\frac{1}{6}$ gr.) in 1 ml. (15 min.).

Dose, as for contained gold salt.

Trade Preparations

Calcium Aurothiomalate. $CaAuSC_4H_3O_4$.

CHARACTERS. Pale yellow powder, insoluble in water. Contains 51·3 per cent. of gold.

Preparation

Collosol Auro-calcium. A finely divided aqueous suspension of calcium aurothiomalate prepared for intramuscular injection.

Dose, 0·025 G. (½ ml.) weekly for three injections; **0·05** (1 ml.) weekly for nine injections; thereafter up to a total of **0·8 G.** according to progress.

Action and Therapeutics

In the treatment of **rheumatoid arthritis,** gold preparations for intramuscular injection are employed extensively. They have no action on the healthy body unless given repeatedly for several days in large doses. They will then cause symptoms of heavy metal poisoning, which include albuminuria, diarrhœa, vomiting, neuritis and various skin rashes. The calcium salt is slowly absorbed from the point of injection and is 100 times less toxic than the sodium preparations as judged by experiments on animals. Patients with rheumatoid arthritis are more susceptible. Certain reactions are liable to arise at any time during treatment, and some may even occur several weeks after its completion.

1. *Immediate.* General malaise, giddiness, and headache of a few hours' duration. Gastro-enteritis.
2. *Focal.* Aggravation of joint pains and swelling after four or five doses. The reaction is a favourable sign.
3. *Rise of temperature.* This may accompany a focal reaction or may follow an injection in a few hours. If it persists for several days, the onset of a digestive disturbance, exfoliative dermatitis, or agranulocytosis may be suspected.
4. *Gastro-intestinal and hepatic.* Abdominal pain, vomiting, and diarrhœa. Jaundice has occurred in epidemic form in arthritis clinics and is probably due to syringe transmission of a virus and not to the gold.

5. *Renal.* Some 80 per cent. of the gold injected is eliminated through the kidneys. This process goes on for several months after the completion of a course. During treatment albuminuria commonly arises; it clears up usually on cessation of treatment. Sometimes renal œdema and massive albuminuria arise and persist for two to three months. This is due to tubular damage—gold nephrosis.

6. *Cutaneous.* Itching, especially on the back of the neck, urticaria, and erythema, particularly on the forehead, occur fairly often. Of rarer occurrence are lichen planus, herpes labialis, and herpes zoster. The most alarming skin reaction is that of exfoliative dermatitis. It is heralded by a simple erythema which gradually becomes œdematous, with a papular and then possibly a vesicular eruption superimposed. Irritation is intense. Death may occur, but recovery is the rule.

7. *Oral.* Sore throat, glossitis, gingivitis, and ulcerative stomatitis have all been reported.

8. *Respiratory.* Bronchitis is reported as arising particularly in association with solganol.

9. *Hæmic.* The hæmopathies are rare but dangerous. Agranulocytosis is the commonest, and may arise quite early in the course of treatment.

It is clearly advisable to examine the urine at least once a week, and to enumerate the white cells every two to three weeks.

It is advocated that two courses of injections be given yearly. Administration is by the intramuscular route, and no local irritant action seems to occur. The progress of the case is indicated by the erythrocyte sedimentation rate. This is always raised in active rheumatoid arthritis, and returns to normal with improvement in the general condition. Some 80 per cent. of sufferers show improvement from correctly administered chrysotherapy.

Idiosyncrasy

All gold salts are liable to produce alarming symptoms in those possessing an idiosyncrasy towards the metal. The most serious is agranulocytosis which may occur after three or four injections or several weeks after the completion of the course. It is characterized by fever, leucopœnia, and ulceration of the throat, and has usually a fatal outcome.

ZINC

Zincum

1. Zinci Chloridum (B.P.C.). Zinc Chloride. $ZnCl_2$.
CHARACTERS. Colourless, opaque rods or tablets, very deliquescent and caustic. *Solubility:* Freely soluble in alcohol, ether, and water if a trace of acid is present.

2. Zinci Sulphas (B.P.). Zinc Sulphate. $ZnSO_4,7H_2O$.
CHARACTERS. Minute colourless prisms. *Solubility:* 10 in 7 of water.

Dose, 10—30 gr. 0·6—2 G. (emetic).

Preparation (**B.P.**)

Unguentum Zinci Oleatis. *Synonym.* Zinc oleate ointment. Zinc sulphate, hard soap, hydrous ointment, and distilled water.

3. Zinci Stearas (B.P.). Zinc Stearate.
CHARACTERS. White, amorphous powder. Insoluble in water.

4. Zinci Oxidum (B.P.). Zinc Oxide. ZnO.
CHARACTERS. A soft, nearly white. tasteless powder, insoluble in water.

Preparations (**B.P.**)

1. **Gelatinum Zinci.** *Synonym.* Unna's Paste. Zinc oxide, gelatin, glycerin and water.

2. **Pasta Zinci Oxidi Composita.** Compound paste of zinc oxide. Zinc oxide 25 per cent. in starch and paraffin (soft).

3. **Unguentum Zinci Oxidi.** Zinc oxide 15 per cent. in simple ointment.

4. **Unguentum Zinci Oxidi Aquosum.** Zinc oxide 15 per cent. in hydrous ointment.

5. **Suppositoria Hamamelidis et Zinci Oxidi.**

Preparation (**B.P.C.**)

Pasta Zinci Oxidi cum Acido Salicylico. *Synonym.* Lassar's Paste. Salicylic acid 2 per cent. with zinc oxide, starch and soft paraffin.

5. Calamina (B.P.). Zinc carbonate coloured pink with ferric oxide.

Preparation (B.P.)

Lotio Calaminæ. Calamine 150, ZnO, glycerin 50, water 1,000.

6. Zinci Peroxidum. *Synonym.* Medicinal Zinc Peroxide. A mixture of zinc peroxide, oxide, and hydroxide.

Action of Zinc Salts

External. The salts, when applied to the broken skin or an ulcerated surface, are all **astringents** and **hæmostatics,** acting by precipitating the albumen in the discharge and also that in the tissues. Thus they resemble lead and silver salts, but as a whole they are less powerfully astringent. The more soluble the salt, the more powerful is its local action. Zinc chloride differs from the other salts in being powerfully caustic.

Internal. *Alimentary canal.* They all have an astringent effect on the gastric and intestinal mucous membranes, and in sufficient quantity produce emesis.

Remote effects. Very little is known about the remote action of zinc salts except from experiments on animals injected intravenously with a double salt. Vomiting, diarrhœa, nephritis, and depression of the nervous system result. The prolonged administration of zinc salts causes loss of appetite and constipation. Workers exposed to the fumes of zinc may suffer from " brass-founders' ague," *i.e.* dry throat, cough, oppressive feeling in chest, vomiting, cramps, rigors, profuse sweating and then deep sleep, from which they awake in normal health.

Therapeutics of Zinc Salts

External. Sticks of zinc chloride are used as caustics. A solution of the sulphate, generally about 2 grs. to 1 fl. oz., usually coloured red with compound tincture of lavender, and then called Lotio Rubra, is applied for its astringent effect to ulcers. Plain solutions of this strength may be applied to the eye for conjunctivitis. The stearate is an excellent application as an ointment to sores and ulcers when a less astringent preparation is required ; and the oxide, either dusted on the parts or used as an ointment, is in constant use for cases in which only a mild astringent effect is desirable. Calamine is an excellent slight astringent for itching skin diseases. Lassar's paste is used extensively in dermatology, especially for dry eczema with much scaling. The salicylic acid component aids removal of the scales. Unna's paste is employed as a dressing for varicose ulcers and eczema.

Internal. *Alimentary canal.* The sulphate is a very good emetic for cases of poisoning, for it acts promptly without causing much nausea and hardly any depression. It is occasionally given as an emetic to children suffering from laryngitis or bronchitis.

COPPER

Cuprum

Cupri Sulphas (B.P.). Copper Sulphate. $CuSO_4, 5H_2O$. *Unoff. Synonyms.* Blue vitriol; Bluestone.

SOURCE. Obtained by the interaction of copper and sulphuric acid.

CHARACTERS. Deep blue crystals in triclinic prisms. Taste, styptic. *Solubility:* 1 in 3·5 of water. Solution strongly acid.

Dose, ¼—2 gr. 16—120 mg. (astringent); **5—10 gr.—0·3—0·6 G.** (emetic).

Action

External. In the solid form copper sulphate is, when applied to raw surfaces, a powerful **caustic.** In dilute solutions it is **astringent** and **hæmostatic,** acting like zinc sulphate, but more powerfully. Copper salts are strongly **antiseptic.**

Internal. *Alimentary canal.* Here also, if very concentrated or given in large doses, copper sulphate is an acute caustic irritant, but poisoning by it is very rare. In medicinal doses it is strongly **astringent.** Five to ten grains of the sulphate form a powerful **emetic,** acting directly on the stomach. As it is more irritating than zinc sulphate, it acts more readily, but it has the disadvantage that, if it fails to act, the stomach must be promptly emptied by some other means, for if not, the copper sulphate will cause inflammation.

Remote effects. Copper salts are slowly absorbed, and copper is re-excreted by the liver in the bile.

Intravenous injection of double salts results in profound depression of voluntary movements and of respiration. Depression of the heart muscle and nephritis also arise.

Therapeutics

External. The sulphate is used as a caustic. Lotions of copper sulphate (0·5 per cent.) may be applied as astringents for just the same purposes as lotions of zinc sulphate ; but it must be remembered that they are more powerful. This is the usual strength for solutions which are to be dropped into the eye.

Copper oleate made, with lanolin, into an ointment of a strength of 10 to 20 per cent. may be used for ringworm.

Internal. Copper sulphate may be used as an **emetic** in 1 per cent. solution, in laryngitis and bronchitis in children, and in cases of narcotic poisoning, for which it is useful on account of its prompt action. It is particularly serviceable in **phosphorus poisoning,** for if it is used copper is deposited on the phosphorus, rendering it inert. It is usual to give three or four grains of the sulphate in water every few minutes till vomiting takes place. After emetic doses of copper sulphate there is generally only one act of vomiting, but by that the stomach is completely emptied. Very little is known about the remote action of salts of copper. It, together with iron, is stored in the fœtal liver, and it is a normal constituent of red cells and serum. It is essential for growth and health, and appears to act as a catalyst for iron in the treatment of secondary anæmia ; it is therefore often prescribed with iron.

Toxicology

In sufficient doses salts of copper are violent gastro-intestinal irritants, but acute poisoning is very rare.

Copper may be taken in very small quantities for a long time without producing any ill-effects, for many persons habitually consume, without harm, preserved vegetables, the green colour of which is due to preparation with copper.

It has been thought that coppersmiths are particularly liable to phthisis, but they are not more prone to it than the followers of other dusty trades. Workers in brass may suffer from anæmia, a green line on and at the bases of the teeth, wasting, weakness, dyspepsia, tremors, headache, vague pains, pharyngeal and laryngeal catarrh with occasional hæmoptysis and aphonia, and profuse secretion of sweat which may be green. These symptoms are thought to be due to the copper contained in brass. Sometimes colic is due to the contamination of copper and brass by lead.

MANGANESE

Manganesium

Potassii Permanganas (B.P.). Potassium Permanganate.
Dose, 1—3 gr. 60—200 mg.
For action see Antiseptics.

Action

It was at one time thought that manganese was essential to hæmoglobin formation, acting in a similar manner to copper. This, however, is not the case. Manganese deficiency if extreme leads to death of experimental animals, and to testicular atrophy and failure of production of the secretion of the anterior lobe of the pituitary gland if the supply of the metal is insufficient.

Therapeutics

Manganese is reputed to raise the bodily resistance to the common pyogenic microbes. It is administered intramuscularly as **Collosol Manganese** (1 c.c.) thrice weekly, and as **Manganese Butyrate,** 1 per cent., in two doses of 1 c.c. at weekly intervals for staphylococcal infections.

Toxicology

The inhalation of the dust of manganese ore or the fumes from the fusing of manganese repeated over a period of about three months rise to definite symptoms arising from toxic action. Manganese is used in the manufacture of steel and other metallurgical processes. The symptoms and signs are as follows :—languor, mask-like facies, monotonous voice, tremor, twitching, and later severe cramps. In advanced cases retropulsion, propulsion and slapping gait develop, as also emotional instability. Blood, urine, C.S.F., and digestive tract are unaffected. There is no disturbance of sensation, whilst on the motor side ankle clonus and brisk tendon reflexes are the only signs of constancy.

The degree of invalidism reached at the time of withdrawal from the poison is permanent, but not progressive.

The causative lesion consists of degenerative changes and gliosis in the basal ganglia, a fact which explains the similarity to paralysis agitans.

There is also a high incidence of pneumonia in workers exposed to the dust of manganese oxides. The dust causes an inflammatory reaction in the bronchioles and alveoli characterized by mononuclear proliferation and infiltration, extensive consolidation of the lung with necrosis and hæmorrhage. Resolution takes place slowly over the course of 9 weeks.

ALUMINIUM

Aluminium

1. **Alumen (B.P.).** Purified alum. A sulphate of aluminium and potassium or a sulphate of aluminium and ammonium.

CHARACTERS. Acid, transparent, colourless crystalline masses, with a sweetish astringent taste. Soluble in water and glycerin.

2. **Kaolinum Ponderosum (B.P.).** Heavy Kaolin. A native aluminium silicate powdered and freed from gritty particles.

CHARACTERS. A soft white powder. *Solubility:* Neither in water nor dilute acids.

Preparation **(B.P.)**

Cataplasma Kaolini. Poultice of Kaolin. Kaolin, 527; boric acid; methyl salicylate; oil of peppermint; thymol; glycerin, 425.

3. **Kaolinum Leve (B.P.).** Light Kaolin.
Purified aluminium silicate.

CHARACTERS. A light, white insoluble powder.

Dose, ½—2 ozs. 15—60 G.

4. **Aluminii Hydroxidum (B.P.C.).** $Al(OH)_3$.

CHARACTERS. White amorphous powder; insoluble in water.

Dose, 5—10 gr. 0·3—0·6 G.

Action of Alum

External. It has no action on the unbroken skin, but coagulates the albumen of discharges from ulcers and sores, and thus forms a protecting covering, and acts as an efficient **astringent.** The albumen in the tissues is coagulated also and this will compress and occlude the vessels, and thus alum is **hæmostatic.** Dried alum absorbs water, and thus its solid form is mildly caustic.

Internal. *Alimentary tract.* Alum acts as an astringent on the mouth, stomach, and intestines, and will cause constipation. In large doses it causes vomiting, acting directly on the stomach, and in larger still, irritant and purgative. Most, if not all, is passed by the fæces; probably, in medicinal doses, it has no remote effects on the tissues.

Considerable controversy has arisen over the possibility of chronic aluminium poisoning from the use of cooking utensils made of this metal. No doubt small quantities are absorbed and stored in the liver, muscles, and kidney. Excretion is in the bile and urine. It is claimed that loss of weight, lassitude and constipation may be thus induced.

Therapeutics of Alum and Kaolin

External. Alum is occasionally used as a caustic to destroy weak exuberant granulations. Kaolin is a good dusting powder. Fuller's earth, also a native aluminium silicate, is used as a dusting powder. Strong solutions of powdered alum applied locally stop bleeding, if it is not severe, such as occurs from slight cuts.

The cataplasma is similar to the familiar Antiphlogistine. The substance is heated by placing its receptacle in hot water, spread on lint and applied to the body as a poultice. It is hygroscopic and thus aids in cleaning up septic areas, and it retains its heat well.

Kaolin resists most chemical reagents, and therefore it is used as a basis for making pills of such bodies as phosphorus, silver nitrate, or potassium permanganate, for with them chemical reaction would occur if an ordinary basis were used.

Internal. *Alimentary canal.* When kaolin is prescribed Light Kaolin shall be dispensed. Only this form is now used for internal administration. As a mouth wash or gargle (0·2 per cent.) alum is valuable in ulcerative **stomatitis,** in aphthous conditions of the mouth, and in slight pharyngitis or tonsillitis, or Glycerinum Aluminis may be painted on with a camel's-hair brush. Kaolin is used to check the diarrhœa of infective enterocolitis and to adsorb intestinal toxins. A suspension of equal parts of kaolin and water is given in half-pint doses half hourly for twelve hours for **cholera** and other infective diarrhœas with success.

It is claimed that aluminium hydroxide, when administered in the form of a gel, is of great value in the treatment of **peptic ulcer.** It differs from alkalis in that, owing to its amphoteric qualities, it will neutralize hydrochloric acid without becoming basic. Aluminium chloride is thus formed without the development of an alkaline reaction. It does not produce alkalosis. Test meals show that it is fairly effective in producing thorough and complete neutralization. The dose advised is 60 to 180 grs. one hour after meals.

IRON

Ferrum

1. Ferrum (B.P.). Annealed Iron wire, diameter 0·1 mm.

Preparations **(B.P.)**

1. Syrupus Ferri Phosphatis Compositus. *Synonym.* Parrish's Food. Iron, 4·3 ; phosphoric acid, 48 ; calcium carbonate, 13·6 ; potassium bicarbonate ; sodium phosphate ; cochineal ; sucrose ; orange-flower water ; distilled water.

Dose, 30—120 min. 2—8 ml.

2. Ferri Sulphas (B.P.). Ferrous Sulphate. $FeSO_4, 7H_2O$.
Characters. Pale green, oblique rhombic prisms, with a styptic taste. *Solubility:* 1 in 1½ of water.

Dose, 3—5 gr. 0·2—0·3 G.

3. Ferri Sulphas Exsiccatus (B.P.). Exsiccated Ferrous Sulphate. Contains not less than 77 per cent. of pure anhydrous ferrous sulphate $FeSO_4$.

Characters. A dirty, white powder which easily absorbs water, and therefore pills made of it may spoil. 3 grs. = 1 gr. of iron.

Dose, 1—3 gr. 60—200 mg.

Preparation **(B.P.)**

Pilula Ferri Carbonatis. *Synonym.* Blaud's pill. Exsiccated ferrous sulphate, 34 ; exsiccated sodium carbonate, 21·6 ; acacia ; tragacanth ; glucose ; water, a sufficiency. This pill contains ferrous carbonate, formed by interaction of ferrous sulphate and sodium carbonate. 30 grs. contain 3 grs. of iron.

Dose, 5—30 gr. 0·3—2 G.

4. Ferri Carbonas Saccharatus (B.P.). Ferrous carbonate, more or less oxidized and mixed with glucose. Contains not less than 50 per cent. of ferrous salts calculated as ferrous carbonate, $FeCO_3$.

Characters. Greenish-brown powder of a sweetish taste.

An unstable compound, easily oxidized. The sugar in both this preparation and in Blaud's pill forms a coating, and prevents further oxidization. The saccharated carbonate should not be given in a mixture, for the sugar is dissolved out, and then the compound can decompose.

Dose, 10—30 gr. 0·6—2 G.

5. **Liquor Ferri Perchloridi (B.P.).** Solution of ferric chloride. Contains 15 per cent. of $FeCl_3$.

Dose, 5—15 min. 0·3—1 ml.

The following is a scale preparation of iron, so called because it is dried to form scales. The base is ferric hydrate.

6. **Ferri et Ammonii Citras (B.P.).** Iron and Ammonium Citrate.

CHARACTERS. Red scales like the tartarated iron, but not so deep in colour. *Solubility:* 10 in 5 of water; almost insoluble in spirit. *Strength:* 40 grs. contain 8 grs. of iron.

Dose, 15—45 gr. 1—3 G.

Action of Iron and its Salts

Iron is essential to the life of every cell in the body for it plays a part, probably as a catalyst, in the oxidative processes of living tissue. It is essential to the production of hæmoglobin.

Distribution in body. There are about 3½ grms. of iron in the body, two-thirds being in hæmoglobin. The liver, kidneys and spleen account for most of the remainder whilst traces are found in the living cells of other organs. It is stored in readily available form in the liver and spleen so that it can be transported to the bone marrow for hæmoglobin requirements.

Source of iron. Normally the daily supply of iron is obtained in organic form in which it exists in relatively large amounts in spinach, watercress and green beans (about 5 mgm. per 100 grms.) and in liver (15 mgm. per 100 grms.) Bread, potatoes and cows' milk contain only a little, but human milk is at least three times as rich in iron (2 mgm. per litre) as is cows' milk. This is a matter of importance in that breast-fed babies seldom suffer from anæmia whilst bottle-fed infants may develop a severe nutritional anæmia. The newborn child starts life with a good store of iron, but on iron-deficient food it will eventually develop anæmia because some iron-loss is taking place by excretion through the large gut. It is estimated that the mother supplies the fœtus and later the child during pregnancy and lactation respectively with iron rising to 2 mgm. daily.

A satisfactory diet for an adult should supply 15 mgm. daily.

Absorption. It seems likely that the complex organic iron compounds consisting of non-ionizable iron have to be broken down into smaller molecules and probably converted into the ionized form before absorption. Inorganic iron is certainly absorbed, possibly only after conversion to the ferrous form. Hæmoglobin which suggests itself as a natural food supply of iron is quite useless in this respect. Iron is not released from it by digestion so that only 20 per cent. of iron in meat is absorbed.

It is possible that ferric iron is reduced in the stomach and duodenum to the ferrous form. This process takes place readily in the presence of easily oxidizable substances such as exist in the food in the stomach and is favoured by an acid reaction. In the absence of HCl. organic acids play their part. When iron reaches the part of the intestine in which the contents are alkaline it is precipitated as insoluble phosphate and can no longer be utilized. In the large intestine the metal combines with hydrogen sulphide and is passed in the fæces as iron sulphide.

It will be seen, therefore, that in the course of its transit through the alimentary tract little time is allowed for its absorption, but this is normally sufficient in view of the small daily requirements of a healthy individual.

Should, however, repeated bleeding occur, iron deficiency will soon show itself and then large doses of the most readily absorbed compounds must be given to make good the loss and to build up depleted reserves. It is of interest to note that women lose from 0·02 to 0·1 grm. of iron monthly. It is estimated that only one-third of iron in food is absorbed, therefore the adult female needs about 10 mgm. iron daily to maintain balance. Repeated small hæmorrhages from piles are another common source of severe iron-deficiency anæmia.

Almost the whole of iron absorption takes place through the duodenum, a little being taken up by the jejunum. It is absorbed intracellularly, possibly by an active process of the epithelial cells. When iron is deficient in the food it is absorbed with avidity. When it is present in plenty over a long period the excess is rejected as if the epithelium were endowed with some discriminating power. A good deal which cannot be utilized or stored is, however, absorbed and then excreted by the epithelium of the large gut.

Excretion. On a normal diet iron is excreted chiefly by the large intestine in amounts up to 8 mgm. daily. On an iron-poor diet this falls quickly to 1 mgm. daily and remains at this level. Practically none of the metal passes out in the urine. If iron preparations be injected intramuscularly there is an increase of intestinal excretion.

Action

Local. Inorganic iron preparations in solution exert an astringent effect. The ferric salts are the most powerful causing precipitation of protein with intense irritation and inflammatory reaction. Iron perchloride is the most powerful in this respect. The teeth and tongue are blackened on account of sulphide formation if iron in solution is taken by mouth.

The œsophagus and stomach may be irritated and give rise to heartburn, abdominal pain and vomiting. The astringent action is continued in the bowel and thus constipation is produced. In some persons the irritant action outweighs the astringency and causes diarrhœa. The ferrous salts may also irritate the stomach and cause symptoms which may be troublesome during treatment.

Iron salts precipitate blood proteins and have thus given rise to fatal embolism when used for injection into nævi. The same action gained them a reputation as styptics, but their use has been superseded by more efficient and less hazardous drugs.

Internal. Headache, giddiness and rarely evidence of true encephalopathy with confusion and excitement may arise from the action of iron on the brain. It seems likely that it indicates an unusual power of absorption of the metal together with an abnormal sensitivity towards its action. Only large and prolonged doses produce it. The two main actions of iron after absorption are the furthering of oxidative processes and the formation of hæmoglobin. Of recent years interest has centred on the latter function by the discovery that it was dependent on the presence of a minute quantity of copper. This metal appears to be necessary for the final stage of hæmoglobin formation. Copper deficiency is very unlikely to occur in the adult, but bottle-fed babies may be short of iron and copper so that the administration of ½ to 1 mgm. of this metal in addition to iron may be found necessary. In Whipple's experiments which ultimately led to the discovery of the liver treatment of pernicious anæmia it was noted that dogs rendered anæmic by repeated bleeding recovered more rapidly on Fe plus liver ash than on Fe alone. The ash contains copper as well as iron.

Therapeutics

The chief use of iron for its local action as an astringent is for **sore throat.** It is often combined with potassium chlorate, *e.g.* liquor ferri perchloridi drachms 2, potassii chloratis grs. 110, aquam ad 8 ozs. ; ½ oz. to be diluted with an equal part of hot water to be gargled and swallowed. It is the swallowing which is advantageous in that the fluid reaches the tonsils and the posterior wall of the pharynx. It is used for the same purpose, though less effectively, as reduced iron lozenges each containing 1 gr. For capillary oozing iron perchloride or a ferrous sulphate solution may be used as a **styptic.**

Five per cent. solutions of iron salts may be employed as astringents in certain forms of **dermatitis,** notably that due to poison ivy. There is a danger, however, of permanent pigmentation of the skin being produced.

The use of iron to check bleeding from the stomach or duodenum is now a matter of historical interest. Even when bleeding comes from minute ulcers associated with gastritis iron would not be suitable because of the irritant action of the soluble salts.

As an astringent to check **diarrhœa** it is far less effective than crude tannin-containing drugs or chalk and opium.

Internal. In the past the outstanding use of iron lay in the treatment of the now vanished **chlorosis.**

Because anæmia was so common in those days it earned a reputation of being a general tonic. Since 1910 chlorosis has been seldom seen.

An equally striking curative effect is seen nowadays in the microcytic, hypochromic, **achlorhydric anæmia** of the middle-aged woman. There is no reason to suppose that it has not occurred for centuries but only recently has the disease been recognized. Response to iron administration is excellent. The absence of hydrochloric acid from the gastric juice is probably of importance here, yet, given sufficient iron, recovery takes place without simultaneous administration of acid. The suggestion that iron is absorbed only after conversion to ferrous chloride is probably incorrect therefore. In conditions of achlorhydria and achylia the pylorus tends to remain open and the stomach and duodenum to empty rapidly. This hurried transit is probably of prime importance in preventing adequate utilization of iron contained in the food.

Iron is indicated for **nutritional anæmias,** *e.g.* in infants fed on cows' milk or any other conditions of insufficient iron intake or absorption. Ascorbic acid deficiency causes microcytic anæmia. Iron should be given in addition to correction of the vitamin lack.

Anæmia due to **hæmorrhage,** especially if repeated, *e.g.* from duodenal ulcer or piles, should be treated with iron because the store in the liver and spleen will have been called upon and may be seriously diminished.

In **hæmolytic anæmias,** *e.g.* malaria, acholuric jaundice, much iron is lost by excretion and its replacement is indicated.

Many acute infections are accompanied by anæmia, and convalescence needlessly prolonged by the failure to recognize the value of iron therapy.

Although the treatment of **pernicious anæmia** consists chiefly of the injection of liver extract it must be remembered that the achylia of this disease favours the non-absorption of iron. Liver treatment restores the red cell count to normal but the hæmoglobin lags behind. Iron therapy should, therefore, be combined with liver treatment.

Choice of iron preparation. From what has been written of the absorption of iron it will be clear that inorganic is preferable to organic iron, and ferrous to ferric salts. The use of iron perchloride has been discussed in relation to its astringent action. It is most unpleasant to take, far less effective than ferrous salts for anæmia and should never be given for this disease.

The scale preparation and various ferrous salts deserve attention. The scale preparation of ferric iron has the advantage of being only slightly astringent and can, therefore, be taken by persons who always suffer from heartburn or other forms of indigestion after taking the simpler compounds. Again the solution is stable, if made with chloroform water, and can be combined with other active drugs apart from mineral acids, fixed alkalis and vegetable astringents. On the other hand, it is relatively costly and must be given in large doses, viz. 90 gr. daily, to be effective. It is of special value in the treatment of anæmia due to bleeding from the stomach or duodenum, or due to gastritis. In such cases it is its relatively non-irritant action which is of importance. Ferrous carbonate is the active principle of Blaud's pill. This is a soluble salt, but prone to conversion to ferric form in solution. In the pill it is mixed with glucose to prevent oxidation. The pills must be of recent manufacture to be effective for they are liable to desiccation and will then pass through the alimentary tract unchanged. Iron carbonate is also present in the Ferri Carbonas Saccharatus (10 to 30 grs.) which is useful for administration to children. It is only slightly astringent, but is hygroscopic. In giving ferrous carbonate not less than 45 grs. should be administered in divided doses daily to the adult.

Ferrous sulphate and ferrous chloride are the most efficient of all the salts. The sulphate and the chloride are both readily utilized and the latter is probably absorbed unchanged.

The effective dosage of the ferrous sulphate is not less than the maximum **B.P.** dose given four times daily. It will be seen that the total needed is very much less than that required for the scale and ferric compounds. In all cases iron should be given after food. It cannot affect the hæmoglobin content of the cells already in circulation, but rather those about to be formed. A lag consequently exists between the beginning of administration and the improvement in the blood picture.

Chlorophyll contains no iron, but closely resembles hæmoglobin in structure. The former is a magnesium-porphyrin, the latter an iron-porphyrin. There is no evidence that chlorophyll alone is of value in correcting anæmia. Green vegetables contain both iron and copper apart from chlorophyll. There is, however, some indication that chlorophyll combined with iron is more effective than the same dose of iron alone. This is of doubtful importance because iron therapy is so excellent in its results.

MERCURY

1. **Hydrargyrum (B.P.).** Quicksilver. Atomic weight, 200·6.

Source. A liquid metal which may be obtained from native mercuric sulphide.

Characters. A brilliantly lustrous fluid metal, easily divisible into small globules.

Preparations (**B.P.**) *containing free mercury*

1. **Hydrargyrum cum Creta.** *Synonym.* Grey powder. *Strength:* 1 of mercury with 2 of prepared chalk.

Dose, 1—5 gr. 60—300 mg.

2. **Tabellæ Hydrargyri cum Creta.** Contain 1 gr.—0·06 G. in each.

3. Pilula Hydrargyri. *Synonym.* Blue pill. Mercury (33 per cent.); liquorice; glucose; glycerin.

Dose, 4—8 gr. 0·25—0·5 G.

4. Unguentum Hydrargyri. *Unoff. Synonym.* Blue ointment. *Strength*: 30 per cent. of mercury.

5. Unguentum Hydrargyri Dilutum. Contains 10 per cent. of mercury.

The B.P. Add. iv directs that this ointment shall be supplied when "Mercury Ointment" or "Blue Ointment" is prescribed unless it be clear that Ung. Hydrargyri is specifically demanded.

6. Unguentum Hydrargyri Compositum. *Synonym.* Scott's ointment. Mercurial ointment; yellow wax; olive oil; camphor. *Strength:* 12 per cent. of mercury.

7. Unguentum Hydrargyri Nitratis Forte. Mercury; nitric acid; lard; olive oil. *Strength:* 6·7 per cent. of mercury.

8. Unguentum Hydrargyri Nitratis Dilutum. 20 per cent. of the strong ointment in yellow, soft paraffin.

Injectio Hydrargyri (B.P.C.). *Synonym.* Mercurial cream. Mercury; wool-fat; camphor; creosote; olive oil. *Strength:* 1 gr. of mercury in 10 min.

Dose, 5—10 min. 0·3—0·6 ml.—by intramuscular injection.

2. Hydrargyri Oxidum Flavum (B.P.). Yellow Mercuric Oxide. HgO.

SOURCE. Obtained by the interaction of aqueous solutions of mercuric chloride and caustic soda.

CHARACTERS. A yellow powder, insoluble in water. Not given internally.

Preparation **(B.P.)**

Oculentum Hydrargyri Oxidi. Yellow mercuric oxide, 1 per cent.

3. Hydrargyri Oxycyanidum (B.P.). Mercuric Oxycyanide. $HgO, 3Hg(CN)_2$.

SOURCE. Interaction of mercuric oxide and mercuric cyanide.

CHARACTERS. White powder, soluble in 18 parts of water. *Strength:* 16 per cent. of HgO: 85 per cent. of $Hg(CN)_2$.

4. Hydrargyri Perchloridum (B.P.). Perchloride of Mercury, Mercuric Chloride. *Synonym.* Corrosive sublimate. $HgCl_2$.

SOURCE. Heat a mixture of mercuric sulphate, sodium chloride, and manganese dioxide. The perchloride sublimes and is condensed.

CHARACTERS. Heavy, colourless masses of prismatic crystals. *Solubility:* 1 in 18 of water : 1 in 3 of alcohol (90 per cent.). It must be dissolved in distilled water, for ordinary water decomposes it.

Dose, $\frac{1}{32}$—$\frac{1}{16}$ gr. 2—4 mg.

Preparation **(B.P.)**

Liquor Hydrargyri Perchloridi. Mercuric chloride; distilled water. *Strength:* 0·1 per cent.; $\frac{1}{10}$ gr. in 110 ♏; 0·1 grm. in 100 millilitres.

Dose, 30—60 min. 2—4 ml.

5. Hydrargyri Subchloridum (B.P.). Mercurous Chloride. HgCl. *Synonym.* Calomel.

Source. Obtained as a sublimate by heating a mixture of mercurous sulphate and sodium chloride.

Characters. A dull, white, heavy, insoluble, nearly tasteless powder.

Dose, ½—8 gr. 30—200 mg.

Preparations **(B.P.)**

1. Tabellæ Hydrargyri Subchloridi. Contain 1 gr.—0·06 grm. in each.

2. Unguentum Hydrargyri Subchloridi. Calomel, 1; hydrous ointment, 4.

6. Hydrargyrum Oleatum (B.P.). Mercuric Oleate.

Source. Yellow mercuric oxide, 20 per cent. in liquid paraffin and oleic acid.

Characters. A light greyish-yellow, oleaginous, semi-solid substance.

Preparation **(B.P.)**

Unguentum Hydrargyri Oleati. Mercuric oleate, 25 per cent. in hydrous ointment.

7. Hydrargyrum Ammoniatum (B.P.). Ammoniated Mercury. NH_2HgCl. *Synonyms.* White precipitate, ammonio-chloride of mercury.

Source. Mix solutions of ammonia and perchloride of mercury. Filter and wash the precipitated ammoniated mercury.

Characters. An opaque, white powder, very insoluble.

Preparation **(B.P.)**

Unguentum Hydrargyri Ammoniati. *Synonym.* White precipitate ointment. Ammoniated mercury, 25; simple ointment, 975.

8. Phenylhydrargyri Nitras (B.P.). Phenylmercuric Nitrate. $C_{12}H_{11}O_4NHg_2$.

Characters. White, crystalline powder. *Solubility:* 1 in 160 of boiling water; more soluble in fixed vegetables oils.

Action of Mercury and its Salts

External. Mercury is a powerful poison, and the general effects are the same no matter what preparation is used. The differences in the action of the various compounds depend upon their solubility and dissociability, and are therefore observed in their local effects and in the readiness with which they are absorbed and thus produce constitutional changes. The **perchloride of mercury** is one of the **most powerful** and important **antiseptics** with which we are acquainted. Thus 1 part in 50,000 will kill infusoria and spermatozoa. Now it is known to be a universal germicide, entering the micro-organism and acting as a direct poison. The antiseptic action is largely dependent upon the number of free mercuric ions present, and therefore freely dissociated salts such as corrosive sublimate act more powerfully than such compounds as mercuric cyanide. The presence of sodium chloride reduces the dissociation of mercuric chloride, and with it its disinfectant action. A solution of 1 in 1000 is very commonly employed for many disinfecting purposes. If organic matter is present in the fluid to be disinfected, the mercury combines with the protein of this and the antiseptic value of the mercury is destroyed. This and the expense of mercurials prevent their use for disinfection of fæces, drains and such-like purposes. The biniodide, dissolved in potassium iodide solution, is a powerful antiseptic.

Phenylmercuric nitrate is a valuable germicide and fungicide. Its toxicity is low and its antiseptic activity is only slightly reduced in the presence of body fluids. It is many times more active than mercury perchloride against Gram-positive cocci. A strength of 1 in 3000 is used for skin disinfection : 1 in 30,000 as a vaginal douche. The closely similar acetate is the most efficient contraceptive available and forms the active ingredient of volpar paste and gels.

Most mercurials destroy the animal and vegetable parasites that infest the skin ; they are therefore **antiparasitic.**

The soluble salts are powerful irritants, for the albuminate of mercury formed is dissolved in the fluids of the tissues, and the acid of the mercurial salt exerts its irritant action ; the acid solution of the nitrate is strongly caustic. Insoluble salts are slightly irritant and stimulating; calomel is sometimes applied to sores for this property.

Metallic mercury and its salts are **absorbed by the skin,** especially when rubbed in either as an oleate or an ointment. These preparations are also taken up, although to a less degree, if simply applied to the skin, for minute particles of mercury or its salts pass into the hair follicles and sebaceous follicles, from which they are absorbed as an oxide or a chloride. All the symptoms of mercurial poisoning can be produced if the drug is absorbed through the skin. The **vapour** can be **absorbed** through the **lungs,** and mercury compounds are so volatile that when they are applied to the skin some usually enters the blood by the lungs.

Internal. Although the different salts of mercury have different external actions, after absorption their actions are, in most respects, similar. The long-continued use of excessive doses of mercurials produces well-marked and important symptoms (*see* Toxicology).

Stomach and intestines. The **metal** mercury itself and **mercurous** compounds, being **mildly irritant** in their action, are often used as **purgatives**; but the mercuric compounds given in the same doses produce severe gastro-intestinal irritation. The metal must be in finely divided form in order to exert any appreciable action. It is for this reason that it is triturated with chalk in grey powder. A globule of mercury of 5 grs. and more would have no effect. It is probable that in divided form the mercury is slowly converted to chloride and sulphide and thus acts as an intestinal irritant. The insoluble mercury subchloride passes through the stomach unchanged, but in the intestine it is slowly converted into soluble form and acts as a mild irritant. Its main action is exerted on the small intestine, but there is also slight stimulation of the colon, in which, however, most of the soluble mercury is precipitated as sulphide. Only a small fraction of the dose taken is rendered soluble in the jejunum, and therefore repeated small doses have more effect than one large one. The green colour of the stools is due to the presence of sulphide, for it occurs even when bile is absent. Purgation usually occurs in six to ten hours, but if this fails an appreciable amount of mercury may be absorbed and symptoms of general poisoning have thus arisen. There is remarkable variation in the degree of response to calomel, one grain producing free evacuation in one individual, whilst five times that dose may be needed to secure the same effect in another.

Liver. It was formerly taught that calomel increased the amount of bile formed by the liver. This is now known to be an error. Calomel and, to a less extent, preparations of metallic mercury are, however, called **indirect cholagogues,** because they aid the expulsion of bile, and being powerful antiseptics increase its purgative action by preventing its decomposition. The stools contain calomel, mercuric sulphide, and unaltered bile.

Remote effects. In large doses mercury irritates the salivary glands and is a powerful **sialogogue.** Minute amounts are excreted by the sweat, milk, and bile. It is in health a relatively feeble **diuretic,** but acts powerfully when dropsy is present. If circulating in sufficient concentration, as after the administration of a soluble salt, it produces acute nephritis. The double salts (Mersalyl) are strongly diuretic when injected intramuscularly or intravenously, yet are far less irritant to the kidneys than are the soluble inorganic salts. The diuretic action is due to increased glomerular filtration and decreased tubular water reabsorption. Mercury accumulates in the body, especially in the liver, kidneys, and spleen.

Excretion. The metal is excreted chiefly in the urine and fæces.

Therapeutics of Mercury and its Salts

External. *Antiseptic action.* Solutions of the perchloride and oxycyanide are employed in a strength of 1 in 1000 for washing infected articles. It must not be used on metal instruments because it corrodes them. For urethral or conjunctival irrigation a solution of 1 in 10,000 may be used, but mercury for such purposes has been superseded by the sulphonamides. Corrosive sublimate solutions should always be tinted blue to render them easy to recognize.

Antiparasitic action. White precipitate ointment, dilute nitrate of mercury ointment, and a wash of the perchloride are very useful for destroying **pediculi**; and these three, especially the last, are excellent for destroying the fungus in ringworm and favus. The mercuric oleate is useful for destroying that in pityriasis versicolor; if the skin is easily irritated the ointment of it should be used. Mercurials should not be applied over so large an area that there is a risk of poisoning from absorption.

Irritant action. The acid solution of the nitrate may be used to destroy warts. Milder preparations, such as the dilute ointment of the nitrate, may be used for tinea. Black wash is used for syphilitic sores and **condylomata.**

Blue ointment and Scott's ointment are used for chronic inflammation of joints, acting as mild counter-irritants. Sixty grains (4 grms.) of blue ointment rubbed into the skin daily, using a different situation each day in the week, is a manner of treating syphilis.

Internal. *Alimentary canal.* By far the most important intestinal action of mercury is its purgative effect. Calomel or blue pill should be given at night and a saline purge in the morning. They are useful for the constipation of fever, but not for regular use. Grey powder is an excellent purgative for children, or even for adults, when a mild purge is required. Children take mercury very well. Infants can easily bear grain doses of the grey powder. As diarrhœa, especially in children, is so often due to the presence of some irritant, grey powder will often cure the diarrhœa. This preparation hardly ever causes griping, but calomel is liable to do so.

Remote uses. In cases of heart disease mercury was often combined with digitalis and squill as a diuretic. The organic mercurials are now used for this purpose, however.

Syphilis. Mercury is powerfully antisyphilitic. It has been mentioned that it may be applied locally to syphilitic ulcerations, but to be of use it is essential that it should also be administered so as to reach the blood. It may be given by mouth as the Liquor Hydrargyri Perchloridi, usually in conjunction with iodide for tertiary syphilis, or by intramuscular injection as Injectio Hydrargyri (10 minims weekly) or by inunction. It is especially valuable in the primary and secondary stages ; also it is of great value in tertiary syphilis. It is as efficacious for the congenital as for the acquired disease. Patients with disease of the kidneys do not bear it well.

In recent years bismuth has largely replaced mercury in the treatment of syphilis.

Sal Alembroth. Ammonio-mercuric Chloride, a double chloride of mercury and ammonium.

CHARACTERS. Flattened rhombic prisms, freely soluble in water or glycerin. Three grains of sal alembroth contain 2 grs. of corrosive sublimate. A powerful antiseptic, not combining with albumen so readily as perchloride, and so less irritating.

Action and Therapeutics

Sal alembroth gauze (1 per cent.) and sal alembroth wool (2 per cent.), both tinted with aniline blue, which is bleached by the discharge, so that it is easy to see if it has soaked through, are used to dress wounds antiseptically.

Mercurochrome. Sodium Dibromo-hydroxy-mercury.

CHARACTERS. Iridescent green scales soluble in water.

Action and Therapeutics

Injected into the bladder as a 1 per cent. solution as an antiseptic. Intravenously 10 to 20 c.c. of the same solution is used in septicæmia and pyelitis with doubtful success. It is also used on the body surface for its antiseptic action.

Mercurial Diuretics

Mersalylum (B.P.). *Tr. Names.* Mercurgan, Salyrgan. The Sodium salt of Salicyl-(y-hydroxymercuric-β-methoxy-propyl) amide-O-acetic acid.

CHARACTERS. White powder ; deliquescent. *Solubility :* 1 in 1 of water.

Preparation (B.P.)

Injectio Mersalyli. Contains 10 per cent. of mersalyl and 5 per cent. of theophylline. The latter is necessary to prevent decomposition of mersalyl in solution, the products of which are toxic. *Strength:* 30 minims contains 3 grs. mersalyl and 1½ grs. theophylline.

Dose, 8—30 min. 0·5—2 ml.

Action and Therapeutics

Until the introduction of organic double salts of mercury the metal could not be used freely for its diuretic effect on account of its toxicity. The official *Mersalyl* and certain trade preparations of similar nature, *e.g. Novasurol*, *Salyrgan*, *Neptal*, *Esidrone*, and *Novurit*, are almost free from this danger and can be injected intravenously or intramuscularly every third day in the treatment of cardiac and renal **œdema, cardiac failure** without superficial œdema and ascites from any cause. They cause increased glomerular filtration and decreased reabsorption of water by the tubules. Theophylline acts in a similar way. They must not be used in the presence of hæmaturia, severely impaired renal function, entero-colitis, fever, or hæmorrhagic states. The usual dose of the various solutions is 2 mils. The addition of theophylline enhances the action.

In cases of **obesity** with water retention in the tissues, mersalyl causes a rapid loss of weight.

For cardiac œdema the injection is given twice weekly and four and two hours previously ammonium chloride 30 grs. are given. This greatly enhances the diuretic effect. Mersalyl is just as effective in producing diuresis whether given with digitalis or not.

Several instances have been reported of sudden death arising as the result of a second intravenous injection of mersalyl. This appears to be due to an anaphylactic reaction which is favoured by the low serum protein of nephritis with œdema. In this disease it should be given intramuscularly only.

Modes of administration of mercurials. **1. By the mouth.** The Liquor Hydrargyri Perchloridi was given to adults, in doses of 1 to 2 fl. dr. (4 to 8 mils). For the later symptoms of syphilis, potassium iodide is combined with it. The oral preparation for children is ½ to 1 gr. (3 to 6 centigrms.) of grey powder, given just often enough to avoid purgation, and 1 to 2 grs. (5 to 12 centigrms.) three times a day is often given to adults.

2. **Endermically.** Mercurials, especially calomel, have been dusted on sores and ulcers, and lotions are also locally applied. Mercury must not be applied in this way if iodides are being administered by mouth lest the corrosive mercury iodide be formed.

3. **By Inunction.** Blue ointment (60 grs.) may be rubbed into the skin. The part of the body should be varied daily: the calves, inner side of the thighs, abdomen, arms, are suitable situations, hairy parts should be avoided. The daily duration of the rubbing is twenty minutes. The ointment has been put inside the sock, for then it is rubbed into the foot during walking. A very efficient way of applying it in children is to smear it on a flannel binder which is worn round the abdomen. The oleate may be employed for inunction. Inunction, if properly carried out, is one of the best means of insuring the absorption of mercury. Inunctions should be given on about fifty consecutive days and then after an interval resumed.

4. **Intramuscularly.** As the official injections.

5. **Intravenous.** As Injectio Mersalyli.

6. **Fumigation.** Calomel is used. The patient, who is naked, sits on a cane-bottom chair; a blanket, which reaches to the floor, is fastened lightly round his neck. Twenty grains of calomel are placed in a porcelain dish over a spirit lamp under the chair. The calomel volatilizes, and is absorbed by the skin. A bath should last twenty minutes.

Toxicology

Acute poisoning is rare. Salts of mercury, especially the per-salts, produce severe gastro-intestinal irritation, causing great pain, vomiting, and diarrhœa. Corrosive sublimate and white precipitate are the preparations usually taken. Acute poisoning has followed washing out large cavities with solutions of perchloride of mercury.

Chronic poisoning by mercury or its salts produces a train of remarkable symptoms. They were very common when it was the practice to give larger doses of mercurials than are now employed, and they are occasionally seen in those who work in mercury. In the present day, when the patient shows any sign of mercurialism, the dose is reduced. These symptoms (which constitute hydrargyrism or mercurialism) may be brought about however the mercury is taken. The first indications noticed are slight fœtor of the breath and soreness of the gums when the teeth are knocked. Then follows a disagreeable metallic taste in the mouth, the gums become swollen and soft, and they bleed readily. Next there is a considerable increase in the amount of saliva secreted. All these symptoms gradually become more marked, and the tongue swells. The teeth are now loose, the saliva, which is thick and viscid, pours over the mouth, the parotid and salivary glands are enlarged and tender, and there is a slight rise of temperature. In olden days these symptoms occasionally ended in the falling out of the teeth, extensive ulceration of the mouth and tongue, necrosis of the jaw, great weakness, emaciation, anæmia, a watery state of the blood, a liability to hæmorrhages, exhaustion, and death.

More rarely the symptoms are, for the most part, nervous. These occur chiefly, if not entirely, among those who work in the metal and inhale the vapour. The first to be observed is tremor, beginning in the face, then invading the arms, and afterwards the legs. Early in the case the trembling is seen only on movement ; soon it is permanent. It resembles paralysis agitans. Usually there is considerable weakness of the affected muscles (" mercurial palsy "). There may be pains, and a weak mental condition is common. Nothing has been found, post mortem, to account for these symptoms.

THALLIUM

Symbol, Tl. Atomic weight, 204

Resembles potassium, lead and arsenic in action on heart-nervous system and skin.

Thallii Acetas (B.P.C.). Thallium acetate ($C_2H_3O_2Tl$).

Dose, 8 milligrms. per kilo of body weight.

Action

In therapeutic doses the only effect is to cause relaxation of unstriped muscle, particularly in the bronchi if previously in spasm. A delayed effect, seen in fourteen to seventeen days, is loosening of the scalp hair which can be easily removed. Larger doses cause falling out of the hair all over the body. Poisonous quantities produce diarrhœa, vomiting, pain in legs and feet, albuminuria, delirium and finally collapse. Chronic poisoning causes stunting of growth, alopecia, and atrophy of the thyroid gland. Toxic symptoms arise more readily in persons past the age of puberty.

Therapeutics

Thallium acetate is used as a depilatory in cases of **ringworm**, and should only be used for this purpose on children under the age of twelve. The drug is given in sweetened water in the dosage suggested above. In this matter the greatest care must be exercised, for slight overdosage may produce alarming symptoms. Ingram advises multiplying the weight of the body in pounds by four ; the resulting figure gives the required dose of thallium acetate in milligrams. If the dose is over 250 mgms. the patient should be treated in bed ; more than 300 mgms. should never be given. The same author advises thrice-daily painting of the whole scalp with 2 per cent. tincture of iodine from the onset of treatment with thallium. The resulting desquamation brings away the loosened hair in the third week, at which stage the head should be washed. Regrowth of hair is rapid.

There is danger from cumulative action, therefore the drug must not be taken again in less than three months.

RADIUM

Radium (B.P.C.). Symbol, Ra. Atomic weight, 226·0

SOURCE. Extracted from pitchblende and other uranium-containing ores; 95 per cent. comes from the Belgian Congo. One part of radium is contained in 5 million parts of pitchblende.

CHARACTERS. A white metal blackening on exposure to air owing to the formation of a nitride. It produces phosphorescence in barium sulphide and other substances. It undergoes atomic disintegration, giving off in the process three types of radiations:

(1) Alpha rays (positively charged helium atoms).

(2) Beta rays (negatively charged electrons).

(3) Gamma rays, which are short electromagnetic waves, and thus of similar nature to X-rays. The total life of radium is about 2600 years. Its degradation products which are always present are termed radon (radium emanation), Radium A, B, C and D. Radon is a gas, the others are solids.

Action and Therapeutics

Local. Radium is a powerful ionizing agent, and decomposes water into its component elements. The alpha rays are responsible for this action, and they cause destruction of the skin, by which they are entirely absorbed. Cancer is apt to arise in such burns. The beta rays are more penetrative, and the gamma rays highly so. The latter are employed chiefly for the treatment of growths. Radium salts or radon are applied to the tissues to be treated in filters which easily stop the alpha and beta rays and which offer resistance to the gamma rays according to their density.

Radium is now used almost exclusively for the treatment of new growths and keloid. The rays have a selective action on actively dividing cells which is probably exerted on the chromosomes, whose injury leads to cell death. Prolonged administration will, however, affect any body cell. Bacteria are very resistant to radium, probably because, though dividing actively, they have no chromosomes.

The results from the use of radium are excellent, particularly for growths in such areas as the uterine cervix and tongue. Extirpation would be mutilating, but under radium the growth shrinks away and leaves a slight scar only. Recurrences of malignant growths and particularly metastatic deposits occur, however, in the majority of cases.

General. The general effect of radium and radium emanation on the body is not seen for several years after its regular administration. Then aplastic anæmia arises and usually leads to death. It is fortunate that the much vaunted radium content of certain Spa waters exists, except in infinitesimal quantities, in the minds of the advertising committee only.

International radium standard. This is 21·99 mgs. of radium chloride, which is in a thin sealed glass tube and kept at the Bureau des Poids et Mesures in Paris.

British radium standard. Twenty mgs. of radium chloride kept at the Nat. Physic. Lab. at Teddington. It expresses activity of specimens in terms of Metallic Radium.

Dose. This varies according to the part to be treated and the form of radium used. Needles containing 1 to 3 mgs. of radium sulphate or bromide, or radon seeds are used.

THORIUM

Thorium is a radio-active element which emits the three types of rays given off by radium. It is only about a millionth part of the activity of this substance however. Its chief interest lies in a derivative known as **Thorotrast.** This is a thorium-dioxide sol which is radiologically visible. The preparation is warmed, and injected intravenously in doses of 20 c.c. daily for two or three days. Sufficient then accumulates in the liver and spleen to render these organs opaque to X-rays. The salt accumulates in the Kupffer cells of the liver, the reticulo-endothelial cells of the spleen, the pulmonary alveolar cells and in the cortical cells of the suprarenals. Some cloudy swelling, and other evidence of toxic damage, is noticeable, but this is much more pronounced in previously diseased organs than in those of an experimental animal. Thorium dioxide remains in the reticulo-endothelial system for many months and is conceivably of danger in reducing the functional integrity of this defensive mechanism. Furthermore, it is slightly radioactive and a spleen from an injected case has produced an image of itself after contact with a photographic plate for 24 hours. This again suggests a potential danger of anæmia similar to that induced by radium. The drug is very valuable experimentally in outlining the arterial system, but

X-rays must be taken during or immediately after arterial injection. Cases of malignant tumour production following the injection of thorotrast into animals have already been recorded, and it seems clear that in view of this danger the drug should never be used on the living human body.

GROUP XXVII

The Metalloids

Bismuth, Arsenic, Antimony, Chromium, and Phosphorus

BISMUTH

Bismuthum

1. Bismuthi Carbonas (B.P.). $2(Bi_2O_2CO_3),H_2O$. *Synonyms.* Bismuth subcarbonate, Bismuth oxycarbonate.

CHARACTERS. A heavy, white powder, insoluble in water.

Dose, 10—30 gr. 0·6—2 G.

Preparation **(B.P.)**

Trochiscus Bismuthi Compositus. Bismuth carbonate heavy magnesium carbonate ; calcium carbonate ; acacia Each contains 2¼ grs. of bismuth carbonate.

2. Bismuthi Præcipitatum (B.P.). Precipitated bismuth. Contains 98·5 per cent. of metallic bismuth.

CHARACTERS. Grey, insoluble powder.

Dose, 1—3 gr. 60—200 mg.—by intramuscular injection.

Preparation **(B.P.)**

Injectio Bismuthi. Precipitated bismuth ; dextrose ; cresol ; water. Fifteen minims contain 3 grs. of precipitated bismuth.

Dose, 8—15 min. 0·5—1 ml.—by intramuscular injection.

3. Bismuthi Salicylas (B.P.). $BiOC_7H_5O_3$. *Synonym.* Bismuth Subsalicylate.

CHARACTERS. A white, heavy powder insoluble in water, alcohol, and glycerin.

Dose, 10—30 gr. 0·6—2 G.
1—3 gr. 60—200 mg.—by intramuscular injection.

Preparation **(B.P.)**

Injectio Bismuthi Salicylatis. Bismuth salicylate ; camphor ; phenol ; olive oil. Contains 2 grs. of bismuth salicylate in 20 minims.

Dose, 10—20 min. 0·6—1·2 ml.—by intramuscular injection.

4. Bismuthi et Sodii Tartras (B.P.). Sodium bismuthyl tartrate. *Synonym.* Bismuth Sodium Tartrate.

CHARACTERS. White powder, freely soluble in water. Contains 40 per cent. of Bi. Neutral to litmus.

Dose, 1—3 gr. 0·06—0·2 G.—by intramuscular injection.

Preparation **(B.P.)**

Injectio Bismuthi et Sodii Tartratis. Contains 60 mg (1 gr.) in 1 ml. (15 min.).

Dose, 1—3 gr. 60—200 mg.

5. Bismuthi Oxychloridum (B.P.). *Synonym.* Bismuth Subchloride.

CHARACTERS. White tasteless powder insoluble in water.

Dose, 10—30 gr. 0·6—2 G.
1—3 gr. 60—200 mg.—by intramuscular injection.

Preparation **(B.P.)**

Injectio Bismuthi Oxychloridi. Bismuth oxychloride; dextrose; cresol; distilled water. Contains 3 grs. of bismuth oxychloride in 30 minims.

Dose, 15—30 min. 1—2 ml.—by intramuscular injection.

6. Bismuthi Subgallas (B.P.). *Synonym.* Bismuth Oxygallate.
CHARACTERS. A yellow powder insoluble in water.

Preparation **(B.P.)**

Suppositoria Bismuthi Subgallatis. Contains 0·3 G. (5 gr.

Action

External. Salts of bismuth have no action on the unbroken skin. Dusted on a raw surface they form a protecting coat, are feebly germicidal, and are very **mildly astringent.**

Internal. If the soluble double salts of bismuth are injected into animals, the symptoms are those of gastro-intestinal irritation and depression of the medullary centres. There is also a direct action on the heart, producing heart-block. It is stated that some very susceptible persons may be poisoned by large doses by the mouth of insoluble salts; but, as a rule, any symptoms of gastro-intestinal irritation caused by the insoluble salts of bismuth are due to the arsenic with which bismuth salts, especially the subnitrate, may be contaminated. When pure, it is probable that these salts, like any bland heavy powder, act chiefly as protectives to the gastro-intestinal mucous membrane. Applied to raw surfaces as dressings, bismuth preparations may produce toxic symptoms which include swelling of the gums and soft palate, black spots in the mouth, vomiting and diarrhœa. They have an **astringent** action, diminishing secretion. The subnitrate in contact with water tends to split up into bismuth oxide and nitric acid, and in the intestine bismuth sulphide is formed, and nitrous vapours are liberated. Any bismuth which is absorbed is excreted chiefly in the urine. It may be found in the liver, kidneys, spleen, and nervous system. Bismuth leaves the rectum as the sulphide, and colours the fæces grey-black.

Therapeutics

External. Salts of bismuth may be dusted on sores as protectives and mild astringents ; the insoluble subnitrate is used for this purpose. Wounds have been dressed with bismuth preparations, and occasionally poisoning symptoms, just described, have ensued.

Internal. The subnitrate and the carbonate are chiefly employed in the treatment of gastric and duodenal ulcer and **diarrhœa.** For ulcer cases they are used in combination with alkalies, *e.g.* magnesium carbonate, and their action is purely protective. For their astringent action they are given in diarrhœa. doses of 60 grs. (4 grms.) being administered without any ill effect.

The salicylate has been used in various gastric affections. It is supposed to combine the virtues of bismuth salts with the antiseptic action of salicylic acid. It easily splits up, and is therefore best given in cachets for summer diarrhœa and cholera.

The subgallate is used principally for its local astringent and protective action in **ulcerative colitis.** A 5 to 10 per cent. emulsion in olive oil or mucilage is run into the rectum at night and retained if possible. More than 12 oz. are seldom tolerated and the action is therefore very localized. It is also used as an **antiseptic** dusting powder, previously known as "dermatol."

The carbonate and oxychloride were used for X-ray work on the alimentary tract, but have been largely replaced by barium for this purpose.

The official injections are used in the treatment of **syphilis.** They are more rapid in action than the mercurials and are less toxic. Bismuth is given in conjunction with the arsphenamines and is of special value in the treatment of tertiary syphilis.

Many of the modern preparations, of which there is a great number, consist of compounds of bismuth and organic arsenic, *e.g.* **bismuth arsphenamine (bismarsen)**, and **bismuth stovarsol (bistovol)** contain 13 and 15 per cent. of arsenic and 24 and 41 per cent. of bismuth respectively.

ARSENIC

Arsenium

Arseni Trioxidum (B.P.). *Synonyms.* Acidum Arseniosum, Arsenious Acid.

CHARACTERS. A heavy, white powder. Contains 99·8 per cent. of As_2O_3. *Solubility:* 1 in 65 of water.

Dose, $\frac{1}{60}$—$\frac{1}{12}$ gr. 1—5 mg.

Preparation **(B.P.)**

Liquor Arsenicalis. *Synonym.* Fowler's solution. Arsenic trioxide, 10; solution of potassium hydroxide; dilute hydrochloric acid; water to 1000. The solution is neutral to litmus. *Strength:* $\frac{1}{12}$ gr. of Arsenic Trioxide in 8 min.

Dose, 2—8 min. 0·12—0·5 ml.

Action of Inorganic Arsenical Compounds

Evidence is accumulating that the toxic effects of arsenic are due to an attack on some essential —SH component in the pyruvate enzyme system. This conception lead to the discovery of BAL (*q.v.*).

External. Arsenious acid has no action on the skin, but applied to raw surfaces it is a powerful **caustic.**

Internal. *Alimentary canal.* Unless the dose is very small, all preparations are very severe **gastro-intestinal irritants.** This is not an ordinary irritation effect for the arsenicals do not precipitate proteins. The mucous membrane of the alimentary tract is, however, red, swollen and shows hæmorrhages. There is fatty infiltration of the mucosa and glands and cloudy swelling of the cells. If given subcutaneously there may be no local effect, although there is intense gastritis soon after injection. In minute doses arsenical compounds are gastric stimulants causing dilatation of the gastric vessels and an increased flow of gastric juice. Small doses also stimulate the duodenum.

Blood. The cellular composition of the blood is altered by the action of arsenic on the bone marrow. The number of red cells falls and immature cells may appear in the peripheral circulation. The polymorphonuclear leucocytes are diminished.

Circulation. Arsenic acts on the capillary walls leading to dilatation of these vessels and increased permeability, particularly in the splanchnic area. This accounts in part for the large amount of fluid in the stools produced by acute arsenical poisoning.

Remote effects. In Styria peasants eat crude arsenic in large quantities as it is believed to improve the state of the skin. It is possible on account of the impure form in which it is presented, and thus only slight absorption takes place. True tolerance is not developed. Large doses cause fatty degeneration, especially of the liver, stomach, and intestines.

Absorption. Inorganic arsenic is absorbed irregularly from the intestine. The soluble forms are completely absorbed and slowly excreted. The drug is thus cumulative. This does not apply to the pentavalent organic arsenicals, *e.g.*, sodium aminoarsenate, tryparsamide and acetarsol, of which some 85 per cent. is excreted in 24 hours.

Excretion. It is eliminated chiefly by the urine, to a less extent by the alimentary canal, the sweat, the saliva, the bile, the milk, hair, cutaneous epithelium, and even the tears, but it is also stored in the body, chiefly in the liver and kidneys. It may be found many years after death in the bodies of those who have taken it during life. It can pass from the mother to the fœtus.

Therapeutics of Inorganic Arsenical Compounds

External. Formerly arsenious acid was used as a caustic to destroy growths, lupus, warts, &c., either pure or as a paste. This use has been superseded by that of diathermy.

Internal. Arsenious acid is useful to destroy the tooth pulps before stopping teeth.

Arsenic is so liable to cause sickness, diarrhœa, and other symptoms of poisoning that it is a rule always to begin a course of it with small doses, say 3 or 4 ♏ (0·18 to 0·25 mil) of the Liquor Arsenicalis, or $\frac{1}{60}$ to $\frac{1}{40}$ gr. (1 to 1·5 mgm.) of arsenious acid as a pill, and gradually to increase the quantity. Arsenic in any form should always be taken immediately after meals, so as to dilute it by the contents of a full stomach. Children bear it well, old people do not.

Arsenic is of value in chronic superficial skin diseases not owing their cause to an irritant. It is, therefore, used for psoriasis, pemphigus, and some forms of chronic eczema.

It reduces the tendency to bromism, and is, therefore, habitually prescribed in conjunction with bromides

Action of Organic Arsenicals

In the early work on atoxyl it was found that it had no toxic action on trypanosomes *in vitro.* This led to the belief that the effectiveness of pentavalent arsenicals in the treatment of protozoal infections was due to their reduction in the tissues to trivalent arsenic in the body. Some organic arsenicals are *pentavalent ;* others contain *trivalent* arsenic. The former group includes Sodium aminarsonate, Tryparsamide, Carbarsone and Acetarsol. To the latter group belong Arsphenamine, Neoarsphenamine, Stabilarsan (a compound of arsphenamine and glucose), Silver arsphenamine, Mapharsen and Sulpharsenobenzene. Pentavalent organic arsenicals are almost wholly excreted in twenty-four hours. Trivalent organic arsenicals are probably oxidised to Mapharsen and owe their action to this substance. They are excreted very slowly, *i.e.* a matter of several weeks. They are stored chiefly in the liver which is apt to suffer in consequence.

Pentavalent Arsenicals

Sodii Aminarsonas (B.P.C.). *Synonyms.* Sodium aminarsonate, atoxyl, soamin, arsamin. A white crystalline powder, soluble 1 in 5 of water.

Dose, ¾—3 gr. 0·05—0·2 G.—by mouth or hypodermically dissolved in water. Even 15 gr. (1 G.) has been given for a single dose.

This compound of aniline and arsenious acid contains about 24 per cent. of metallic arsenic, but much larger doses of it than of ordinary arsenical preparations can be given without symptoms of poisoning. It is efficacious, especially when tartar emetic is also given, for trypanosomiasis. It does not affect trypanosomes outside the body, but its action in the body is due to its reduction to arsenic in the trivalent state. Many cases of poisoning are on record; the symptoms are dryness of the throat, headache, vomiting, diarrhœa, and in some cases total blindness due to optic atrophy. Injections are given subcutaneously—rarely intravenously—at intervals of two or three days.

Acetarsol (B.P.). *Synonym.* Acetarsone. *Tr. Name.* Stovarsol. $C_8H_{10}O_5NAs$. Contains not less than 27·4 per cent. of pentavalent As.

CHARACTERS. White crystalline powder moderately soluble in boiling water.

Dose, 1—4 gr. 60—250 mg.

Carbarsonum (B.P.). This drug is p-Carbamino-phenylarsonic acid.

CHARACTERS. White crystalline solid, insoluble in water.

Dose, 2—3 gr. 0·12—0·2 G.—by mouth.

Tryparsamidum (B.P.). Tryparsamide is Sodium-N-Phenylglycineamide-p-Arsinate.

CHARACTERS. Colourless crystalline powder, freely soluble in water.

Dose, 15—30 gr. 1—2 G.—by subcutaneous, intramuscular, or intravenous injection.

Preparation (B.P.)

Injectio Tryparsamidi.

Dose, as above. Must be freshly prepared.

Therapeutics

Acetarsol can be given by mouth. It is used for the treatment of syphilis, yaws, and **amœbic dysentery.** It is less effective than neoarsphenamine in syphilis, but may be used to treat the congenital disease in children or whenever injections are inadvisable. The sodium salt can be injected intravenously or intramuscularly in gramme doses twice weekly to a total of 20 grms. Such a prolonged course is recommended for general paralysis of the insane. Acetarsol tablets are very effective if introduced vaginally in the treatment of **vaginitis** due to *Trichomonas vaginalis.*

Carbarsone is used for **amœbic dysentery** in the chronic stage. Arsenic is slowly liberated in the gut and is absorbed. The usual course is 0·25 grm. twice daily for ten days.

Tryparsamide is widely used in the treatment of sleeping sickness (**trypanosomiasis**), and has replaced sodium aminoarsonate because it is less toxic. It is highly effective in sterilizing the blood, glands and cerebrospinal fluid of patients infected with *T. gambiense.*

Even the nervous symptoms are greatly relieved by treatment.

Permanent cure has been reported in about a third of the cases treated. It is usual to give a weekly dose of 3 grms. intravenously for eight to ten weeks and repeat the course after four months. The first course alone will usually abolish the cerebrospinal lymphocytosis which is seen in the second stage of the malady. These figures relate to the infection prevalent in the Belgian Congo. The effect of tryparsamide on *T. rhodiense* has been studied in Tanganyika and found unfortunately to be very slight.

Tryparsamide is the drug of choice for the treatment of **neurosyphilis.** It appears to penetrate the central nervous system far more effectively than do the trivalent arsenicals. A course consists of twelve weekly injections (*i.v.*) of 2 to 3 grms. each according to weight and reaction.

Blindness may arise from the use of this drug due to selective action on the optic nerves. In the majority of patients nearly all the drug is excreted in twenty-four hours. In others this is delayed and toxic signs are apt to arise.

Trivalent Arsenicals

Arsphenamina (B.P.C.). *Tr. Names.* Arsenobenzol, Kharsivan, Salvarsan, Arsenobillon, It is chemically dioxydiaminoarsenobenzol dihydrochloride. It is often called " 606 " because that was its number in a series investigated.

Characters. A bright yellow powder, slowly but completely soluble in water. Strongly acid, contains about 30 per cent. arsenic. Supplied in glass tubes, filled with an inert gas to prevent oxidation. The tube should not be opened until immediately before administration as, on exposure to air, the drug becomes toxic.

Dose, 0·1—0·6 G. The amount usually contained in each tube is 0·6 G. Given intravenously but superseded by neoarsphenamine.

Neoarsphenamina (B.P.). Neoarsphenamine. *Tr. Names.* Neosalvarsan, Novarsenobillon, Neokharsivan. A condensation product of formaldehyde sulphoxylate of sodium and salvarsan. Known as " 914," as that was its number in a series investigated.

Characters. A yellow powder, sold in glass tubes filled with an inert gas to prevent oxidation which rapidly renders it toxic. It has the great advantage of being freely soluble in water, forming a neutral solution. Cold water must be used, as warm water decomposes the drug. 1·5 G. neosalvarsan equals 1 G. salvarsan. Standardized by biological assay. Contain 20 per cent. of As.

Dose, 2½—10 gr. 0·15—0·6 G.—by intravenous injection. Dissolved without heating, and with very little shaking, in 10 c.c. of freshly distilled water, given intravenously.

Preparation (**B.P.**)

Injectio Neoarsphenaminæ.
Preparation and dose as above.

Arsphenamina Argentica (B.P.C.). *Synonym.* Silver arsphenamine. A dark brown powder, soluble in water and of alkaline reaction.

Dose, 0·1—0·3 G.—intravenously.

Sulpharsphenamina (B.P.). *Synonym.* Sulpharsenobenzene.
Characters. Yellow powder, soluble in water.

Dose, 1½—10 gr. 0·1—0·6 G.—by subcutaneous or intramuscular injection.

Preparation (**B.P.**)

Injectio Sulpharsphenaminæ.

Dose, 1½—10 gr. 0·1—0·6 G.—by subcutaneous or intramuscular injection.

Sulphur compounds of " 914 " are useful arsenical preparations for syphilis, as they are suitable for intramuscular or deep subcutaneous injection, and are not painful.

Combination of arsenic with bismuth has been referred to in dealing with the latter substance.

Mapharsen. CHARACTERS. White amorphous powder containing 29 per cent. of trivalent arsenic. It is soluble in water and alcohol. It is hygroscopic and marketed in nitrogen-filled ampoules.

Dose, 0·04 G. rising to **0·06 G.** in 10 ml. distilled water intravenously, weekly, for 10 doses.

The small amount of arsenic to the effective dose, as compared with the arsphenamines, and the greater rate of excretion make this the best arsenical for the treatment of syphilis.

Therapeutics

Syphilis. Arsenicals are of use in acquired or congenital syphilis ; they cannot restore structures already destroyed, but will prevent the progress of the syphilis. Their use causes the spirochætes to disappear, and the Wassermann reaction may become negative. Sometimes transient pyrexia follows with headache, vomiting, rigors, fall of blood pressure followed by œdema and urticaria—the *nitritoid crisis.* More serious are encephalitis hæmorrhagica, hæmorrhagic nephritis, agranulocytosis, aplastic anæmia, dermatitis and jaundice. If there is serious disease other than syphilis, and especially if of the liver, these drugs should either be withheld or given carefully in small doses.

The *Jarisch-Herxheimer reaction* is liable to occur after the first injection of an arsphenamine. It is due to the widespread destruction of spirochætes and the focal inflammatory responses in the tissues caused thereby. It consists of rigor, pyrexia, malaise, aching in the limbs (general response) and intensification of syphilitic inflammatory (focal) reaction, *e.g.* aggravation of cutaneous or mucosal lesions in secondary syphilis, or swelling of the intima and media of the aorta with coronary occlusion and death. In cardiovascular syphilis it may also lead to rupture of an aneurysm or cerebral thrombosis or hæmorrhage. In syphilis of the larynx it may cause asphyxia. To prevent it iodides must be given for three weeks before arsenicals are injected.

If syphilis be treated in the first stage, complete cure is probable. Once general invasion has taken place this result is far less certain, whilst in tertiary and nervous syphilis cure cannot be expected, although considerable amelioration of symptoms may be brought about. Usually ten arsenical doses are given at intervals of a week, with weekly intramuscular injections of mercury or bismuth. The course-dose of arsenical is 6 grms.; that of bismuth is 3 grms. The course is given four times in the first year and in the intervals 1 grm. of iodide is given thrice daily. Treatment in the second year is according to the stage of the disease and the response to treatment. These arsenicals have been used for **relapsing fever,** in which a single dose of neoarsphenamine may suffice, **Vincent's angina,** both intravenously and locally, **yaws** and **rat-bite fever.** They have been reported favourably upon in the treatment of anthrax.

Toxicology

Acute Poisoning. White arsenic is frequently used as a poison. Soon after taking it the sufferer experiences faintness, nausea, sickness, epigastric pain and tenderness. These symptoms quickly increase. The vomit is brown, and often streaked with blood; the pain is very severe; there is profuse diarrhœa, with much tenesmus; and there are cramps in the calves of the legs. The vomiting becomes violent and incessant; there is a burning sensation in the throat, with intense thirst. Soon severe collapse sets in; the skin is cold, the pulse small and feeble, and the patient dies. The symptoms frequently bear a close resemblance to those of cholera. *Post mortem.* The stomach is intensely inflamed, even if the arsenic has not been taken by the mouth, but has been applied in large quantities to cancerous growths. This shows that arsenic is excreted from the blood into the stomach. The small intestines are also acutely inflamed.

Treatment. Wash out the stomach. The stomach must be completely emptied. Give unlimited quantities of freshly-prepared humid peroxide of iron or dialysed iron. If neither of these is handy, give magnesia in large amounts. Restore fluid-loss with intravenous saline. Inject morphine. Apply hot blankets and bottles to the feet and the abdomen, and give hot coffee.

Chronic Poisoning. Often, when arsenic is taken as a medicine, slight symptoms of poisoning are seen. They are loss of appetite, nausea, perhaps vomiting, slight abdominal pain, and mild diarrhœa. The eyelids become a little puffy, the conjunctivæ injected, the eyes and nose water, and there is slight headache. These symptoms, of course, show that the dose given is too large, and that it must be decreased.

Arsenic is so often used in the manufacture of all sorts of articles, especially wall papers and fabrics, that chronic poisoning by it is frequently seen. It is also met with in workers in arsenic, and in persons to whom it has been given with intent to murder. The symptoms produced are those already mentioned as present when large doses of arsenic are taken medicinally.

Long-continued use of arsenic may induce peripheral neuritis ; the chief symptoms of arsenical neuritis are herpes zoster, paralysis of the muscles of the limbs, especially the extensors of the hands and feet, ataxic gait, severe darting pains in the limbs, and rapid muscular atrophy. Several cases are recorded in which arsenic has caused general brown pigmentation of the skin, best marked about the neck. Very rarely pigment forms in the mucous membrane of the mouth. It may also give rise to a general increase of epidermic scales (keratosis) and to brown pigmentation of patches of psoriasis, and in quite exceptional cases cause eczema or urticaria. The tongue may be silvery. After death from chronic poisoning, in addition to the gastro-intestinal and nervous lesions, there is widespread fatty degeneration of most of the organs of the body. It is well seen in the liver, kidneys, stomach, and muscles, including the heart.

BAL (British anti-lewisite) is 2, 3-dimercapto-propanol, an oily substance soluble in 16 parts of water. It was devised as a highly efficient antidote to the local effects of lewisite.

Trivalent arsenicals inhibit the pyruvite enzyme system leading to a rise of blood pyruvate such as occurs in vitamin B_1 deficiency. Their toxicity is due to their combining with —SH groups. BAL prevents this and will reverse it.

Intramuscular BAL, 4 mg./kg., 4-hourly is used in the treatment of arsenical dermatitis and encephalitis and also in gold dermatitis.

ANTIMONY

Antimonium. Atomic weight, 120·2

1. Antimonii et Potassii Tartras (B.P.). Tartarated Antimony. $(KSbO, C_4H_4O_6)_2, H_2O$. *Synonym.* Tartar emetic.

SOURCE. Prepared from antimonious oxide and acid potassium tartrate.

Characters. Colourless transparent crystals with triangular facets. *Solubility:* 1 in 17 of cold, 1 in 3 of boiling water. The solution is faintly acid.

Dose, $\frac{1}{32}$—$\frac{1}{8}$ gr. 2—8 mg.
$\frac{1}{2}$—1 gr. 30—60 mg. (emetic).
$\frac{1}{2}$—2 gr. 30—120 mg.—by intravenous injection.

Preparation (**B.P.**)

Injectio Antimonii et Potassii Tartratis. Contains 20 mg. ($\frac{1}{3}$ gr.) in 1 ml. (15 min.).

Dose, $\frac{1}{2}$—2 gr. 30—120 mg.

2. Antimonii et Sodii Tartras (**B.P.**). Antimonyl Sodium Tartrate.

Characters. A white, crystalline powder, freely soluble in water.

Dose, $\frac{1}{32}$—$\frac{1}{8}$ gr. 2—8 mg.
$\frac{1}{2}$—1 gr. 30—60 mg. (emetic).
$\frac{1}{2}$—2 gr. 30—120 mg.—by intravenous injection (in 2 per cent. solution).

Preparation (**B.P.**)

Injectio Antimonii et Sodii Tartratis. Contains 60 mg. (1 gr.) in 1 ml. (15 min.).

Dose, $\frac{1}{2}$—2 gr. 30—120 mg.

Action

External. Antimonial compounds are powerful external **irritants.** Tartar emetic produces a **pustular eruption** at the point of application.

Internal. *Alimentary canal.* All compounds of antimony are powerful **irritants,** internally as well as externally; the action of **tartar emetic** is best known. The first result of swallowing this is **vomiting.** The early acts of vomiting are entirely due to the direct action of the drug on the wall of the stomach, but after it is absorbed, by its action on the medulla it also produces sickness; but this action is slight. It will cause vomiting when injected into the blood, a little by its action on the medulla—for it will act if the stomach is replaced by a bladder—but chiefly because some of it is excreted into the stomach and intestines, and thus the vomiting is continued for some time. In large doses tartar emetic is irritant to the intestine.

Remote effects. These are seen only after intravenous injection, to which the following account refers.

The rapid pulse, pallor and sweating seen after administration by mouth are referable to the emesis only.

Heart. Antimony is a powerful **cardiac depressant,** diminishing both the frequency and the force of the beat of the heart. The cardiac depression causes the arterial pressure to fall, but part of this effect is due to a coincident action upon capillaries, as by arsenic.

Respiration. Respiration is depressed, the movements become weaker, and inspiration is shortened, but expiration is prolonged. Finally, the pauses become very long and the movements very irregular.

Nervous system. Depression is produced partly by action in the cord and medulla, largely indirectly through the effect on the circulation.

Temperature. Moderate doses hardly affect the temperature, but large doses cause a **considerable fall,** owing, no doubt, in the main to the circulatory depression.

Excretion. Antimony is excreted into the stomach, intestines and urine.

If its use is continued for some time it will cause, like arsenic, fatty degeneration, especially of the liver, and abolition of the hepatic glycogenic function.

Therapeutics

Internal. *Alimentary canal.* Tartar emetic is not to be recommended as an **emetic,** for the action is slow, and the general depression of emetic doses is great. Ipecacuanha is preferable.

Respiration. It is rarely used as an **expectorant** in acute bronchitis.

Antimony is poisonous to protozoa. A 2 per cent. solution of tartar emetic is given intravenously for Kala-azar (Leishmaniasis) and sleeping sickness (trypanosomiasis). The first dose is 2 c.c., and 1 c.c. is added at each bi-weekly dose until 10 c.c. is reached. **Bilharziasis** is successfully treated the same way by injecting 1 or 2 grs. for each dose till 30 grs. have been given. Intensive treatment with antimonyl sodium tartrate has been shown to give excellent results in both vesical and intestinal forms of schistosomiasis (Bilharziasis). The total dose is 12 mgm. per kilo of body-weight ($\frac{1}{10}$ gr. per lb.) given in three injections on two successive days. One grain (0·06 grm.) is made up to 10 c.cm. in 5 per cent. glucose-saline and administered slowly (not less than five minutes) intravenously. Toxic reactions are rare. Seventy per cent. of antimony given in this way is found to remain in the body after seventy-two hours. Slowing of the heart is not produced with the sodium salt: it is probably referable to the K ion. Tartar emetic intravenously is also useful for filariasis, yaws, and oriental sore and relapsing fever.

Stibophenum (B.P.). *Tr. Name.* Fouadin.

Dose, 1½—5 gr. 0·1—0·3 G.—by intravenous injection.

A soluble salt of antimony used principally in the treatment of **schistosomiasis** (Bilharziasis) and of **granuloma inguinale.**

A 90 per cent. recovery from vesical schistosomiasis can be achieved from the intramuscular injection of a total of 0·5 G. (0·04 G. daily for 6 days in each of 2 consecutive weeks).

Preparation **(B.P.)**

Injectio Stibopheni. Contains 0·3 G. (5 gr.) in 5 ml. (75 min.).

Dose, 25—75 min. 1·5—5 ml.—by intravenous injection.

Stibosan (von Heyden 471) and Neo-stibosan (von Heyden 693b) are pentavalent antimony preparations which have proved to be of great value in the treatment of Kala-azar. The latter substance is particularly effective and less toxic than its congeners. Stibosan is given intramuscularly thrice weekly, starting with 0·05 G. and rising to 0·3 G. with total dosage of 2·5 G.

Neo-stibosan may be given intramuscularly, 0·3 G. in 25 per cent. solution daily for eight days. Nausea, vomiting and pain do not occur with this compound. In resistant cases it may be given intravenously.

Toxicology

Acute Poisoning. The symptoms are very like those of arsenical poisoning. *Post mortem.* The gastro-intestinal irritation is very similar, but less marked.

Treatment. Unless the vomiting is very free, the stomach-pump may be used. Also frequent doses of tannic acid or magnesia. Hot-water bottles and warm blankets.

CHROMIUM

Chromium

Chromii Trioxidum (B.P.). Chromic Acid. Chromic anhydride. CrO_3.

CHARACTERS. Crimson acicular crystals, very deliquescent, soluble in water. Readily yields oxygen, and will therefore easily explode. It does so with either glycerin or alcohol.

Action

External. In consequence of its oxidizing power chromic acid is a powerful deodorant and disinfectant. It coagulates albumen and oxidizes organic matter, and is therefore a powerful **caustic.**

Internal. Chromic acid is an astringent and irritant.

Therapeutics

External. As a lotion, 1 in 40, or even stronger, chromic acid has been used for its disinfectant properties to wash foul ulcers and sores, and also as a local application for ozæna, gonorrhœa, leucorrhœa, and bad ulceration of the mouth. A 5 per cent. solution may be used as a mouthwash for pyorrhœa, or as a gargle for acute tonsillitis. When employed in this strength it should be followed at once with a wash of hydrogen peroxide.

PHOSPHORUS

Phosphorus (B.P.C.).

CHARACTERS. A wax-like solid, freely soluble in carbon bisulphide, sparingly soluble in alcohol, ether, and chloroform, 1 in 80 in olive oil or melted fat, insoluble in water ; luminous in the dark. Must be kept under water, as it oxidizes and takes fire very easily. Heated with hydrogen it forms red or amorphous phosphorus, which is non-poisonous, as it is so insoluble that it cannot be absorbed.

Dose, $\frac{1}{100}$—$\frac{1}{25}$ gr. 0·0006—0·0025 G.

Preparation (B.P.C.)

Oleum Phosphoratum. Phosphorus dissolved in almond oil. *Strength:* One per cent.

Dose, 1—5 min. 0·06—0·3 ml. (in a gelatin capsule).

Action

The only known action of minute doses of phosphorus is that in animals it causes the deposition of a layer of dense bone at the growing point which replaces the cancellous tissue. If larger, frequently repeated doses are given for some time, proliferation of the interstitial connective tissue of the stomach, liver, and kidney is also found, and fatty degeneration of the organs (*see* Toxicology). Phosphorus enters the blood as phosphorus, and acts as such, not as phosphoric acid. The rate of its absorption depends upon the fatty acids in the intestine. It is eliminated in the urine in organic combination, and also to some extent in the expired air.

Therapeutics

It has been used in osteomalacia, in rickets, and in cases of ununited fracture, but it is of little use in medicine and no longer appears in the Pharmacopœia.

Toxicology

Acute Poisoning. Phosphorus is taken, or administered criminally, either as match heads or vermin paste. For the first few hours there are no effects, then the following symptoms of gastro-intestinal irritation set in: Nausea, abdominal pain, and vomiting; the vomited matters smell of phosphorus and are luminous. There is some general depression. Diarrhœa is rare. The patient may die of collapse, but far more frequently these symptoms all pass off, and he appears quite well. But after three or four days jaundice is noticed, and this soon becomes very deep; there is now great prostration, the liver is enlarged, the abdomen distended, and he complains of intense thirst. Vomiting of altered blood and diarrhœa with bloody stools may be observed, but these two symptoms are not severe. The skin is cold, the pulse feeble and rapid. The urine is scanty, highly coloured, albuminous, bile-stained, and perhaps bloody; it contains the acetone bodies and lactic acid, and in the final stages may contain bile acids and crystals of leucin and tyrosin. There is an excessive protein metabolism, as shown by the increase of sulphates, and nitrogen in the urine. This last comes from the excess of ammonia which is produced in the protein tissues and poured into the blood to neutralize the lactic acid and the acetone acids, which appear because phosphorus prevents the complete oxidation of glycogen, fat, and the non-nitrogenous results of protein breakdown. This incomplete oxidation leads to the accumulation of fat in the liver and the muscles which undergo fatty degeneration. Muscular twitchings occur, the patient becomes comatose and dies. *Post mortem.* Two results are very striking. (1) Fatty degeneration (thus phosphorus resembles arsenic and antimony), affecting principally the liver, in which it is very marked; and if the patient lives long enough there may be a diminution in size of the organ. Fatty degeneration is also found in the muscles, kidneys, and gastro-intestinal tract. (2) Hæmorrhages are seen in many places, and ecchymoses are sometimes very abundant. The symptoms of phosphorus poisoning in many respects resemble those of acute yellow atrophy of the liver.

Treatment. Thoroughly empty the stomach by a stomach-pump or by washing it out. Give copper sulphate as an emetic, 3 gr. (2 decigrms.) every few minutes till vomiting is induced, then every fifteen minutes. No oils or fat should be given. A full dose of a saline purge may be administered.

Chronic Poisoning. This, which used to be seen in those who worked among phosphorus fumes, is now of great rarity. The chief symptoms are those of gastro-intestinal irritation and necrosis of the jaw.

Hypophosphites of Calcium and Sodium

These drugs are valueless, and are excreted unchanged in the urine.

Glycerophosphates. These compounds are rapidly decomposed and the phosphates excreted in urine and fæces, whilst the glycerin is oxidized. Recent work has shown that they aid in the process of fat absorption from the intestine.

GROUP XXVIII

HORMONE PREPARATIONS

Class A. Endocrine Preparations, including Sex Glands.
Class B. Hormones of the Digestive System.

Nature. Hormones are chemical compounds elaborated by the secretory cells of endocrine glands. Some of these compounds, such as the sex hormones, have been isolated in pure crystalline form either from the glands in which they are built up or from the body fluids in which they circulate or are excreted. Some have been synthesized in the laboratory and may, therefore, be obtained in a condition of absolute purity. The chemical composition of such hormones is known exactly. Others, such as the pituitary hormones, have so far largely resisted isolation in crystalline form and attempts at chemical synthesis, and are available therefore only as extracts of varying purity and are standardized by biological assay.

Action

Since these substances are natural products of normally functioning endocrine glands, the healthy organism receives an adequate endogenous supply, and the exogenous administration of additional quantities tends in most cases to be without effect. Little therefore may be said of the "*action*" of many of the hormones, and it is only in animals or individuals deprived of the activity of the gland concerned that the effect of the hormone becomes demonstrable.

Modes of Administration

A proper understanding of the relative efficacy of the various modes of administration of hormone preparations is becoming increasingly important as new routes come into popular use. In the following account an attempt has been made to indicate the method of choice, taking into consideration the extent to which the chemical structure of each hormone affects its absorption into the blood stream.

1. *Oral.* Œstrogenic, progestogenic and androgenic activity can be obtained by oral administration. The synthetic œstrogens should always be taken by mouth because they are as active by this route as by injection, and considerably more active in equivalent doses than the natural œstrogens when given orally. This and their relatively low cost have led to their popularity. Their tendency to produce mild toxic effects such as nausea and headache is a contra-indication in some cases, in which the natural œstrogens will be preferred. Androgenic activity by the oral route is obtained by giving methyl testosterone and progestational effects may be produced by the oral use of ethisterone. Thyroid, stomach and liver extracts are also active by mouth. Apart from these hormones, however, there is not available at the moment sufficient evidence to justify the use of oral preparations of any other hormone, and the prescription of the compound pill or polyglandular concoction containing hormone extracts in unstandardized doses is as unscientific as it is expensive.

2. *Sublabial or sublingual.* Certain of the steroid hormones such as œstrogens, androgen and desoxycorticosterone have recently been given in the form of small tablets placed under the tongue or between the gum and upper lip. These tablets dissolve in the course of half an hour and the active principle is

absorbed through the mucous membrane into the blood stream. The mode of administration causes the patient very little inconvenience and absorption is said to be more effective than by the alimentary tract.

3. *Snuff.* Posterior pituitary extract may be made up in small packings of 20 mgm. or more in the form of a powder to be placed in a special insufflator which may be introduced into the nostril. The powder can then be sniffed up and the fine granules will adhere to the mucous membrane lining the nose from which the active principle will be absorbed. This mode of administration is used in the case of posterior pituitary extracts in diabetes insipidus and has the advantage that injections which are dreaded, especially by children, are avoided and the daily dose may be divided into frequently administered portions.

4. *Vaginal suppositories.* This route has been used in the case of œstrogens for the treatment of local conditions such as pruritus, kraurosis and atrophic vaginitis due to œstrogen deficiency. It has the advantage that relatively low doses can be given which, though effective in relieving the local condition, are less likely to produce undesirable general effects such as tenderness and swelling of the breasts.

5. *Inunction.* This method is also employed, chiefly in the case of œstrogens, either in the form of an alcoholic solution or as an ointment. Its main indication is for underdeveloped breasts. It is claimed to have a high degree of local activity and to be capable, therefore, of administration in relatively small doses which are unlikely to produce undesirable general effects such as disturbances of the menstrual cycle.

6. *Injection.* (1) Subcutaneous. Substances which are soluble in water and are unlikely to cause local reactions may be injected subcutaneously, for instance insulin, adrenaline, posterior pituitary extract and parathyroid hormone.

(2) Intramuscular. Intramuscular injection is preferred for hormones which are soluble in oil and those hormone extracts which because they contain proteins

are liable to give rise to painful reactions at the site of injection, such as anterior pituitary extracts. The oil-soluble substances, are the so-called "steroid" hormones.

The pure hormones have a relatively transient effect and would certainly require daily injection to maintain anything like a constant level of activity. If, however, an ester of the hormone is used there is considerable prolongation of the duration of effect. Thus the compounds most usually employed are œstradiol benzoate and œstradiol dipropionate, testosterone propionate and desoxycorticosterone acetate. The esters need to be injected only once or twice a week (except when desoxycorticosterone acetate is being used during a crisis in Addison's disease). Unfortunately it is not possible to esterify progesterone, which must be administered daily or at least every other day to be effective.

Intramuscular injections of crystalline suspensions. Minute crystals of œstrogens and androgens have been put up in aqueous suspension for intramuscular injection. It is claimed that absorption from the surface of the crystals continues at a constant level of effectiveness for a longer period than intramuscular injection of the oily solution.

(3) Intravenous. Adrenaline is occasionally given intravenously (or directly into the heart muscle) in cases of extreme cardiac emergency because of its very transient effect on subcutaneous injection. Thyroxine has been employed intravenously in rare cases of acute myxœdema. Natural cortical extract is used with normal saline by the intravenous route in the crises of Addison's disease, and serum gonadotrophin has been said to be less likely when thus administered to result in failure in cases of sterility due to defective spermatogenesis or anovular bleeding.

7. *Implantation.* The subcutaneous implantation of pellets of compressed or fused crystals of the steroid hormones is now an established mode of administration. The method, however, should still be reserved for those who have had some experience of it. Strict

asepsis is essential in introducing the pellet. Nevertheless, in spite of this some hormones or their compounds (for instance, progesterone and testosterone propionate) are often extruded through the skin. The advantages of this method are that the hormone activity persists for some months, that the absorption from the pellet is at a constant rate, and that there is no wastage of hormone, as there is bound to be when other routes of administration are employed, so that implantation is the most economical method of hormone administration conceivable. A word of caution should be added however, on the subject of prolonged continuous administration of sex hormones, especially œstrogens. In high dosage there may be serious and perhaps irreversible inhibition of anterior pituitary activity. Though there has so far been no evidence of the carcinogenic properties of œstrogens in human beings, one of the essential features of experimental carcinogenesis produced by œstrogens in animals is that the hormone should be given continuously and over very long periods. As a 100 mgm. pellet of compressed œstradiol may take over two years to be absorbed, such therapy may be said to be continuous over a long period. The implantation technique has been employed so far in the case of œstrone, œstradiol, œstradiol dipropionate, stilbœstrol, progesterone, ethisterone, testosterone, testosterone propionate and desoxycorticosterone acetate. Pellets have been used in a variety of shapes and sizes ranging from 15 to 350 mgm. It is as yet too early to set down a standard of dosage.

Unfortunately non-steroid compounds, such as insulin and the pituitary hormones, do not show the characteristic feature of slow absorption when subcutaneously implanted, and it is therefore not as yet a suitable method to apply to them.

CLASS A

THYROID GLAND

Thyroideum (B.P.). *Synonyms.* Dry Thyroid. Thyroid Extract.

SOURCE. A powder prepared from the fresh and healthy thyroid gland of the sheep. One part of dry thyroid is approximately equivalent to 5 parts of the fresh gland.

CHARACTERS. A cream-coloured powder, with faint meat-like odour and taste, and free from odour of putrescence. Deteriorates in the presence of moisture.

COMPOSITION. The active principle is thyroxine, which contains 65 per cent. of iodine. Thyroid contains 0·1 per cent. of iodine in combination as thyroxine.

Dose, ½—2 gr. 30—120 mg.

Preparation (**B.P.**)

Tabellæ Thyroidei. Each contains ½ gr. (30 mg.).

Thyroxinum. Thyroxine.

SOURCE. Synthetic.

CHARACTERS. White crystalline powder, insoluble in water.

COMPOSITION. Contains 65 per cent. of iodine.

Dose, $\frac{1}{120}$—$\frac{1}{64}$ gr. 0·5—1 mg.

Di-iodotyrosinum. Di-iodotyrosine.

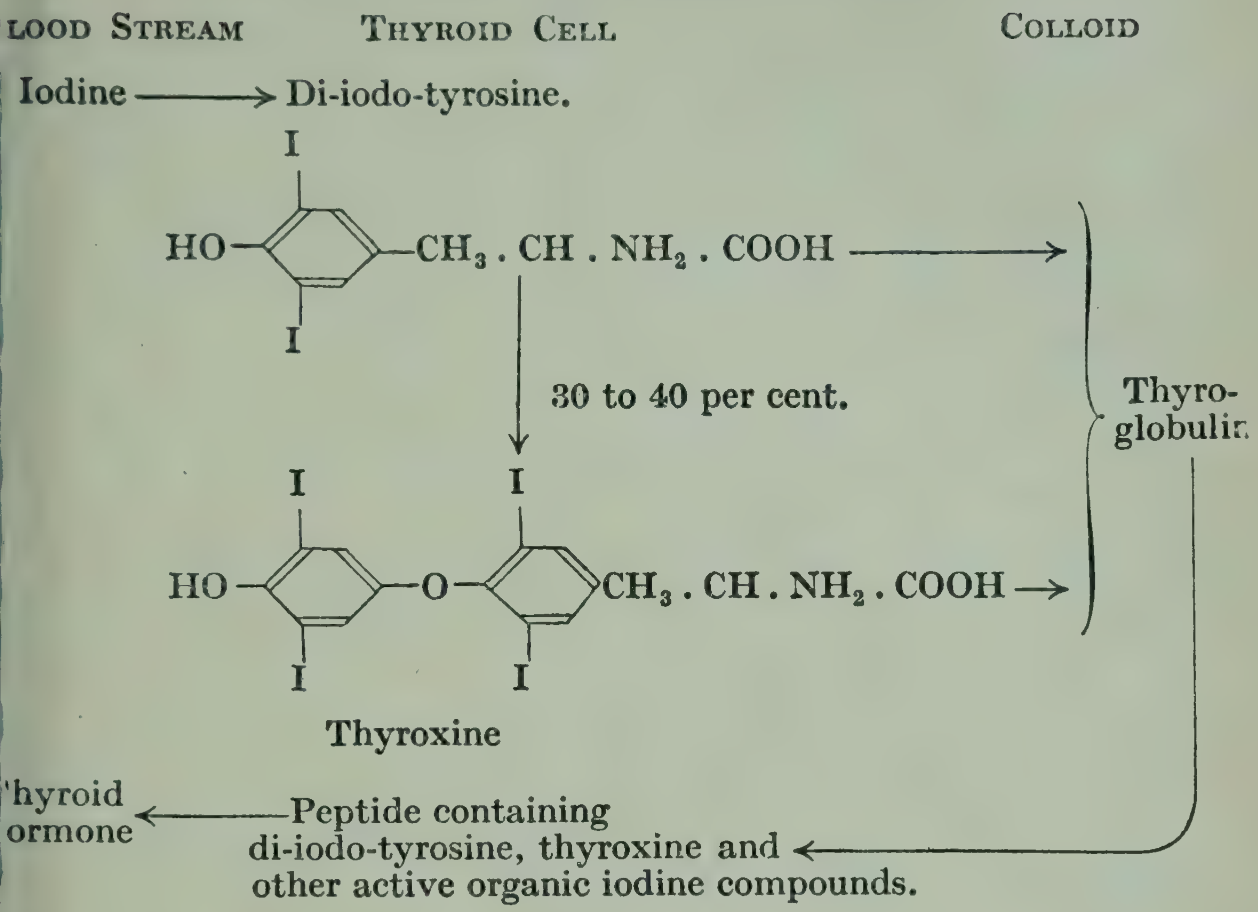
SOURCE. Synthetic.

CHARACTERS. White crystalline powder.

Dose, 1½ gr.—0·1 G.

Iodine compounds of the thyroid. The cells of the thyroid gland are supplied from the blood stream with iodine in inorganic form. This enters into combination to form di-iodotyrosine, 30 to 40 per cent. of which undergoes condensation to thyroxine. Both these organic compounds are stored in the colloid as thyroglobulin. On reabsorption into the thyroid cell this protein becomes hydrolysed with the liberation of a peptide containing thyroxine, di-iodotyrosine and other active organic iodine-containing compounds of unknown composition. This peptide represents the true active principle of the gland.

Iodine Compounds of the Thyroid Gland


LOOD STREAM
THYROID CELL
COLLOID
Iodine
Di-iodo-tyrosine.
I
HO
CH₃ . CH . NH₂ . COOH
I
30 to 40 per cent.
Thyro-
globulir
I
I
HO
O
CH₃ . CH . NH₂ . COOH
I
I
Thyroxine
'hyroid
ormone
Peptide containing
di-iodo-tyrosine, thyroxine and
other active organic iodine compounds.

Thyroideum (**B.P.**) is standardized to contain 0·1 per cent. of *iodine in combination as thyroxine* on the incorrect assumption that thyroxine is the only active iodine-containing compound of the thyroid. A total organic iodine standard is employed by some manufacturers.

Action

The effect of thyroid hormone on normal subjects is variable and unpredictable. There is little indication for its use in such individuals and its "action" is therefore unimportant. Such effects as it does produce are usually due to overdosage. Observations on thyroidectomized and normal animals and on human subjects suffering from thyroid disorders have shown that the hormone is a general metabolic stimulant.

Therapeutics

The most striking results of thyroid hormone therapy are seen in **cretinism** and **myxœdema,** in which there is a lowered basal metabolic rate, a high blood cholesterol and a myxœdematous infiltration of the subcutaneous tissues. Maintained administration of the appropriate dose of thyroid in such cases leads to dramatic changes in the patient's appearance. Thyroid medication is commonly employed in **obesity.** When the treatment is combined with dietary restriction, appreciable though usually temporary loss of weight may be achieved when such doses are given as may lead to the appearance of certain of the well-recognized toxic symptoms. In cases in which the obesity is associated with water-salt retention thyroid extract is sometimes efficacious on account of its diuretic properties.

This diuretic effect of thyroid hormone has been observed in myxœdema and has suggested its use in **nephrosis** which is associated with a low basal metabolic rate and a high blood cholesterol, though unlike myxœdema a low serum protein value is found in this condition. Beneficial results are sometimes observed. Improvement is seen in some cases of **arthritis** in which thyroid would appear to act locally as a non-specific metabolic stimulant. Its mode of action in certain **disorders of the skin** is probably similar. Senile eczema, ichthyosis, scleroderma and nutritional disturbances of the nails and hair may benefit from administration of thyroid extract. Improvement in hearing has been reported in ear and nerve **deafness.** The beneficial results obtained in Ménière's syndrome are probably due to the dehydrating effects of the hormone on the tissues of the internal ear. Finally, thyroid extract plays an important part in the treatment of **menstrual disorders,** especially when they are associated with a low metabolic rate. In view of the disappointing results of treatment of certain types of menstrual disorder with sex hormones thyroid extract is worth a trial. The ætiological factors in **sterility** and **habitual abortion** are so numerous and varied that the alleged beneficial effects of thyroid extract should not be ignored in planning the complicated therapeutic *régime* which is commonly employed for these conditions.

Thyroid hormone has a delayed action and a cumulative effect. A single dose of 1 mgm. of thyroxine will produce its maximum effect on the basal metabolic rate in a case of thyroid deficiency a week after administration and will take another week to pass off. The hormone is just as efficacious therefore when given in a single daily dose as when administered thrice daily. Owing to its cumulative action the administration should be discontinued from time to time for a few days, the dose administered should be chosen with care, and the patient should be under constant medical supervision, so that symptoms of overdosage may be promptly recognized. On rare occasions it may be necessary to place the patient under immediate therapeutic control, as for instance in acute myxœdema. The intravenous administration of thyroxine is valuable for this purpose. Apart from this, thyroxine has no advantage over the more usually employed preparation of dry thyroid extract. There is considerable individual variation in response to thyroid extract. Those cases which show obvious signs of thyroid deficiency usually respond to relatively low doses and 1½ to 2 gr. daily are sufficient to produce dramatic improvement on most cases of **cretinism** and **myxœdema.** Some obese patients are relatively intolerant to the hormone, and quite small amounts lead to symptoms of overdosage. On the other hand, the majority of such individuals can tolerate 5 or 6 gr. daily without showing any untoward effects, though such doses usually indicate that thyroid hormone medication is unlikely to produce a specific effect. Especial caution should be exercised with ambulant patients and with those suffering from cardiac disorders, and initial doses of ½ to 1 gr. daily should be increased only gradually at weekly or fortnightly intervals. The presence of septic foci or acute infective diseases lowers the patient's tolerance to the hormone and is a possible cause of symptoms of overdosage.

Toxicology

The best criterion for controlling the dose of thyroid extract is the pulse rate. So long as it remains under 90 per minute there is no danger in maintaining the dose prescribed. Early signs of overdosage apart from tachycardia are palpitations, a fine tremor of the outstretched fingers, nervousness and headaches. Sweating, nausea, diarrhœa and rapid loss of weight follow. Auricular fibrillation may occur especially in patients with pre-existent myocardial damage. Emaciation and exophthalmos occur only after prolonged overdosage.

Thiouracilum (B.P.). $C_4H_4ON_2S$. A white bitter powder, slightly soluble in water.

Dose, 1½—3 gr. 0·1—0·2 G.

Preparation (**B.P.**)

Tabellæ Thiouracili. Contain 0·1 G.

Methylthiouracilum (B.P.). $C_5H_6ON_2S$.

Dose, 1½—3 gr. 0·1—0·2 G.

Preparation (**B.P.**)

Tabellæ Methylthiouracili. Contain 0·1 G.

Propyl Thiouracil. Dose, 0·05—0·6 G.

The use of thiouracil is now well established as a method of treatment of **thyrotoxicosis.** After a latent interval of a week or so there is a rapid drop in pulse rate and the basal metabolic rate falls to normal within a few weeks, with a corresponding rise in blood cholesterol. There is marked improvement in the clinical picture and the patient regains weight. Thiouracil and certain other sulphur-containing compounds such as the sulphonamides act by preventing the formation of thyroxine and the consequent production of thyroid hormone. This lack of secretion of the active principle of the gland stimulates the anterior pituitary to increase its thyrotrophic effect so that the histological picture of the thyroid gland is one of hyperplasia and lack of colloid. The extent to which production of the thyroid hormone is inhibited depends directly on the dose of thiouracil. The initial dose of thiouracil is from 0·4 to 0·6 gm. The dose is gradually diminished as the pulse rate and BMR are lowered and symptoms abate and the maintenance dose is 0·05 to 0·1 gm. daily. The compounds are given in divided doses three or more times daily in order to provide a more even effect.

At the time of writing thiouracil and its compounds have not yet established themselves as the best method of treatment of hyperthyroidism. There are some who still prefer partial thyroidectomy in all circumstances, some who lean towards iodine in the treatment of mild cases or for pre-medication in operative cases, some who condone thiouracil only as a pre-operative measure, whereas others confidently advocate thiouracil as the sole treatment for all established cases of hyperthyroidism. It is as yet too early to express strong views on the subject. There is no doubt that thiouracil must be used with caution, and that overdosage or disregard of warning symptoms such as sore throat and pyrexia may lead to disastrous results. Cases of agranulocytosis heralded by these symptoms have been recorded. They usually develop suddenly, on relatively high doses and early in the treatment. Leucopænia, and especially granulocytopænia, are contra-indications for pushing thiouracil treatment, but are not necessarily forerunners of agranulocytosis, so that it is unnecessary to demand repeated blood pictures in order to forestall agranulocytosis. In addition to the possible danger of agranulocytosis, various toxic manifestations of thiouracil treatment such as skin rashes present themselves in 25 per cent. of cases. Though, up to now the death-rate from agranulocytosis in recorded cases of thiouracil treatment is no more than the operative mortality of thyroidectomy, it is well to emphasize that the drug treatment demands prolonged and skilled medical attention.

PARATHYROID

Extractum Parathyroidei (B.P.C.). *Synonyms.* Parathormone; Euparatone. 20 units per c.c. (**B.P.C.**). Paroidin. 100 units per c.c. (**U.S.P.**).

Source. Obtained from fresh parathyroid glands of healthy animals. The aqueous extract of the active principle is purified, and sterilized by heating.

Standardization. The unit is one hundredth part of the amount required to raise the blood calcium of a dog by 5 mgm. per 100 c.c. The **U.S.P.** unit is one-fifth of the **B.P.C.** unit.

Dose, 20—40 units—by injection.

Action

Parathyroid extract raises the serum calcium, increases relatively and absolutely the amount of ionized calcium in the blood, lowers the blood phosphorus and increases the excretion of both calcium and phosphorus. The lower the serum calcium the more effective is parathyroid extract in raising it. For instance, 15 units (**B.P.C.**) a day may raise the serum calcium from 4·5 to 7 mgms. per 100 c.c., whereas it may require 100 units to raise the level from 10 to 12 mgms. per 100 c.c. (The normal serum calcium value is 9 to 11 mgms. per 100 c.c.)

Therapeutics

The chief indication for the use of parathyroid extract is **tetany.** This is associated with a diminution of the total serum calcium or, as in the tetany due to alkalosis, a diminution of the ionized calcium. Tetany results from spontaneous hypoparathyroidism and removal of parathyroid tissue at an operation for thyroidectomy; increased utilization or defective absorption of calcium, as in rickets, osteomalacia and steatorrhœa; and alkalosis, due to pulmonary hyperventilation, pyloric or high intestinal obstruction associated with persistent vomiting and loss of chloride ions, or over-dosage with alkalies. Treatment consists in restoring the serum calcium figure by (1) administration of parathyroid extract which mobilizes calcium from the bones, (2) administration of dihydrotachysterol, a derivative of ergosterol, which increases the absorption of calcium from the gut and the urinary excretion of phosphorus, (3) administration of calcium in the form of one of its salts, either by mouth, intramuscularly or intravenously, and (4) facilitating the absorption of calcium by administration of vitamin D.

For the following reasons the therapeutic value of parathyroid extract is limited: it is ineffective when given by mouth, and its maximum effect is attained only about four hours after intravenous injection; it is therefore useless for terminating an acute attack, which can, however, be controlled by the intravenous injection of calcium. Parathyroid extract is more effective when given in divided doses than when administered in the form of a single dose. Its administration should be controlled by frequent serum calcium estimations. After some months of repeated injections the hormone begins to lose its effect. This limits its use to acute conditions.

Toxicology

Not only does the serum calcium level rise above the normal figure, but there is an increase in the inorganic phosphorus. Metastatic calcification occurs in soft tissues such as the lungs and the kidney. Renal function is impaired and the blood urea rises. Osteoporosis results from excessive mobilization of calcium from the bones.

ADRENAL GLAND

Medulla

Adrenalina (B.P.). Adrenaline. *Synonyms.* Adrenalin, Epinephrine.

It is dihydroxyphenylmethylaminoethanol. $C_6H_3(OH)_2.CHOH.CH_2.NH.CH_3$.

SOURCE. Prepared as an acid extract of the adrenal glands of certain mammals, or by synthesis.

CHARACTERS. A light brown or nearly white, crystalline powder. Sparingly soluble in water; insoluble in alcohol and ether; unstable in neutral or alkaline solution. Rapidly destroyed in the body.

Dose, $\frac{1}{600}$—$\frac{1}{120}$ **gr. 0·1—0·5 mg.**—by subcutaneous injection.

Preparations **(B.P.)**

1. **Liquor Adrenalinæ Hydrochloridi.** Adrenaline, 1; chlorbutol, 5; sodium chloride; sodium metabisulphite; dilute hydrochloric acid; distilled water to 1000. To be preserved in amber glass bottles.

2. **Injectio Adrenalinæ.** *Synonym.* Injection of Adrenaline Tartrate. Contains 0·1 per cent. of adrenaline.

Dose, 2—8 min. 0·12—0·5 ml.

Action

Adrenaline has no action on the unbroken skin, but acts locally when applied to serous or mucous membranes, *e.g.* that of the nose. It is very rapidly destroyed in the body and is consequently not absorbed in active form when given by mouth. It is usually injected subcutaneously, and the effect is so immediate that it is seldom necessary to give it intravenously.

Adrenaline acts on all structures innervated by the sympathetic nervous system, at the nerve-endings of which an *adrenergic* substance is liberated when the sympathetic nerve is stimulated. The sweat glands are supplied by sympathetic nerves, but a *cholinergic* substance is liberated at their nerve endings on stimulation. Adrenaline therefore has no action on the sweat glands.

Heart. The rate and the force of the beat are increased from stimulation of the cardio-accelerator nerve-endings in the heart muscle. The increased output and rise of blood pressure distends the aorta and carotid sinus, thus sending impulses *viâ* the cardio-inhibitor centre causing subsequent slowing of the heart beat. Adrenaline decreases the refractory period of heart muscle and thus makes it more liable to fibrillate under the influence of chloroform.

Vessels. The blood is redistributed to the vital organs and structures by the action of adrenaline. The spleen contracts, thereby increasing the circulating blood volume. The peripheral arterioles and those of the splanchnic area constrict, leading to a *rise of blood pressure.* Constriction of the small vessels is especially marked at the point of local application, *e.g.* when adrenaline is applied to the mucous membrane of the nose. The vessels of the lungs, heart and brain are little affected by even large doses of adrenaline, the chief effect, which is secondary to the rise of blood pressure, being slight passive dilatation.

Lungs. The bronchi are relaxed, especially when they are in a state of spasm, as in asthma.

Liver. Glycogen is mobilized and converted to glucose, with a tendency to hyperglycæmia and glycosuria.

Eye. The pupil is dilated, the upper lid retracted and the eyeball may be protruded, when adrenaline is injected intravenously in animals. The action corresponds to that produced by stimulation of the cervical sympathetic yet it is actually intensified when the nerves have been allowed to degenerate.

Intestine. The sphincters are closed and the walls of the gut relaxed, so that the movements of the intestine are diminished.

Bladder. The sphincter is constricted, and the bladder wall relaxed.

Uterus. The effect on the uterine muscle varies in different species. The human uterus is stimulated.

Skin. The vessels of the skin are constricted and the hairs erected from contraction of the arrectores pili muscles.

The majority of these effects are produced only after intravenous injection of adrenaline in experimental animals.

Therapeutics

Because of its powerful local vaso-constrictor action an aqueous solution of adrenaline—of a strength of 1 in 1000—may be locally applied as a **hæmostatic** in epistaxis or before operations on the nose and throat. For these purposes it may be used as gauze plugs soaked in the 1 in 1000 solution, or as a spray (1 in 2500). It may be introduced into the bladder as a pre-operative measure. Applied with cocaine substitutes which of themselves fail to cause vaso-constriction, it may be used for painless, bloodless operations on the eye and other parts. It is useless to apply it to the brain or lungs for this purpose because its action is very feeble where the blood vessels are not normally controlled by the sympathetic nervous system.

As adrenaline is rapidly destroyed in the intestines it can be given for its remote effects hypodermically or intravenously only.

Adrenaline, by its action on the bronchi, will effectively terminate a paroxysm of **asthma.** Five minims of the Liquor injected subcutaneously may accomplish this in a few seconds. Subcutaneous injection of adrenaline may also be beneficial in acute urticaria and other **anaphylactic phenomena.**

Adrenaline may be injected subcutaneously in cases of sudden **cardiac failure**, for in animals the heart may be completely resuscitated by this method, even when the circulation has apparently ceased. Intracardiac administration has occasionally restored the heart beat after its cessation on the operating table. Only 3 or 4 minims of the liquor should be used. It may be used with advantage for the Stokes-Adams syndrome of **heart block.** It may also be used in the treatment of **insulin coma.**

Toxicology

Symptoms of over-dosage or intolerance are dizziness, a bursting feeling in the head, vomiting, excitement and convulsions. The rapid rise of blood pressure which is one of the normal actions of the drug is harmless in the healthy individual, but may cause considerable strain on arteriosclerotic vessels. Continued administration of the drug, however, is unable to *cause* arteriosclerosis owing to the transience of its effect. Patients under chloroform anæsthesia are especially sensitive to the cardiac action of adrenaline, and ventricular fibrillation is more liable to occur in such circumstances.

Cortex

Extractum Suprarenalis Corticis (B.P.C.). Extract of Adrenal Cortex. *Synonyms.* Cortin ; Eschatin ; Eucortone ; Supracort.

SOURCE. Prepared from the adrenal glands of cattle, by extraction with alcohol, benzene and acetone.

COMPOSITION. The extract contains the active principle, corticosterone ($C_{21}H_{30}O_4$) and is free from vitamin C ; less than 1 in 1,000,000 adrenaline must be present.

STANDARDIZATION. Numerous methods of standardization are in use, such as determination of the amount required to maintain life or health in adrenalectomized rats, cats, dogs or drakes, or to restore the response to faradic stimulation of the gastrocnemius muscle of the adrenalectomized rat, and corresponding units are described. Doses, however, are still generally referred to in c.c. of the liquid preparation.

Dose, 5—40 units—by injection.

Deoxycortoni Acetas (B.P.). *Synonym.* Desoxycorticosterone acetate. This is a synthetic preparation from stigmasterol of the active principle. *Tr. Names.* Cortiron ; Doca ; Percoten. 5 mg. corresponds in potency to 10 c.c. of cortical extract.

Dose, $\frac{1}{30}$—$\frac{1}{6}$ gr. **2—10 mg.**—by intramuscular injection.
3—6 gr. **0·2—0·4 G.**—by implantation.

Preparation (B.P.)

Injectio Deoxycortoni Acetatis. 5 mg. in 1 ml.
Dose, $\frac{1}{30}$—$\frac{1}{6}$ gr. 2—10 mg.

Action

Recent studies of the functions of the adrenal cortex have shown that it produces hormones (1) which maintain life and protect the organism against stress, (2) which influence the metabolism of sodium, potassium, chloride and water (desoxycorticosterone), (3) which exert an influence on carbohydrate metabolism, mainly by building up liver and tissue glycogen, (4) which have androgenic properties and can be demonstrated in the urine as 17-ketosteroids, and (5) which have œstrogenic and progestogenic properties. Cholesterol and vitamin C are found in the adrenal cortex, and it is believed that certain adrenal cortical hormones are derivatives of these compounds.

Therapeutics

The main indication for use of adrenal cortical extract, or the synthetic compound desoxycorticosterone acetate which is now more generally employed, is **Addison's disease.** Its chief value is in the crisis which are characteristic of this condition, where the natural gland extract should be given in doses of 20 to 25 ml. daily by the intravenous route slowly with saline with additional doses of up to 40 mg. or more of desoxycorticosterone acetate. In severe cases of adrenal cortical deficiency it may be necessary to administer desoxycorticosterone in doses of from 5 to 10 mg. daily by the intramuscular or subcutaneous route even in the intervals between crises, though in the majority of cases, a healthy state may be maintained by giving sodium chloride in 10 to 20 G. doses daily by mouth. To avoid daily injection the method of subcutaneous pellet implantation in doses of 200 to 600 mg. has been employed beneficially though overdosage should be avoided as it may lead to œdema.

PITUITARY GLAND

Pituitary (Posterior Lobe) Extract

Injectio Pituitarii Posterioris (B.P.). *Synonym.* Pituitary Extract. *Tr. Names.* Glanduitrin; Hypophysin; Piton; Pitoxylin; Pituitrin. This is prepared from the posterior lobe of the pituitary body of oxen or other mammals.

Dose, 3—8 min. 0·2—0·5 ml. (2—5 units)—by subcutaneous or intramuscular injection. Standardized by biological assay.

Pituitary (Posterior Lobe) Powder. *Tr. Names.* Di-sipidin; Piton: for insufflation. Piton is in the form of 500 units per gram in lactose.

Oxytocin. *Synonym.* α-hypophamine. *Tr. Names.* Pitocin; Orasthin; Uteritrin. A solution of the oxytocic principle of the posterior lobe of the pituitary, free from the pressor principle.

Preparation (**B.P.**)

Injectio Oxytocini. *Synonym.* Oxytocin. Contains 10 units per ml.

Dose, 8—15 min. 0·5—1 ml. (5—10 units)—by subcutaneous or intramuscular injection.

Vasopressin. *Synonym.* β-hypophamine. *Tr. Names.* Pitressin; Pitressin tannate; Tonephrin; Tonitrin. A solution of the pressor and anti-diuretic principle of the posterior lobe of the pituitary, free from oxytocic principle.

Preparation (**B.P.**)

Injectio Vasopressini. *Synonym.* Vasopressin.

Dose, 8—25 min. 0·5—1·5 ml. (5—15 units)—by subcutaneous or intramuscular injection.

Action

Mode of administration. Pituitary extract has no effect when given by mouth. It is rarely, if ever, necessary to inject it intravenously owing to its rapid action by the subcutaneous or intramuscular routes. A more prolonged effect (up to thirty-six or forty-eight hours from a single injection) may be obtained by use of the tannic acid ester. Satisfactory results are also obtained by use of a powder which may be administered by high nasal insufflation in doses of 50 to 300 units (50 to 300 mgm.) daily, the insufflation being performed every six or eight hours. The powder is used for its anti-diuretic effect.

1. **Oxytocic effect.** *Uterus.* The oxytocic effect of

pituitary extract varies according to the species investigated. In the guinea-pig the uterine muscle always responds by contraction, and this is the method used for biological assay of the oxytocic factor. In the rabbit the response of the uterus to oxytocin appears to be facilitated by œstrogens and inhibited by progesterone. In the human being, oxytocin has little or no effect before parturition.

2. Pressor effect. *Circulatory system.* Injection of pituitary extract into the normal individual produces a marked pallor due to constriction of the peripheral arterioles. There is a **rise of blood pressure** depending in extent on the previous blood pressure level. If normal, the subsequent rise is negligible. If low, the rise is considerably more marked, and repeated injections give rise to diminishing pressor responses.

Kidneys. In the anæsthetized animal vaso-pressin exerts a **diuretic effect.** The response obtained in the normal animal and human being is an **anti-diuretic effect.** This is best demonstrated by the delay which occurs in urinary secretion after large volumes of water have been drunk, when pituitary extract has been previously administered. The effect is produced by direct action on the epithelium of the tubules resulting in increased absorption of water.

Mammary glands. The so-called *galactogogue* effect of posterior pituitary extract is not due to stimulation of milk secretion but to the expression of milk previously secreted in the alveoli owing to contraction of the smooth muscle surrounding the ducts.

Intestines. Administration of pituitary extract increases intestinal motility in the intact animal, and to a less degree in the normal human individual.

Stomach. The secretory activity of the gastric mucosa is inhibited, so that for some hours after an injection there is a diminished secretory response to histamine. Gastric ulceration has been produced by experimental administration of pituitary extracts.

Bladder. The smooth muscle of the bladder wall contracts.

Therapeutics

1. *Oxytocin.* Either pituitary (posterior lobe) extract or its oxytocic factor is used in obstetrics. It is employed especially during and immediately after parturition, and its use should be avoided in the first stage of labour, or when there is any suspicion of mechanical obstruction to delivery as there is some danger of rupture of the uterus. It may be given in the second stage, but is best reserved to **control post-partum hæmorrhage** and to ensure proper uterine contractions. It is frequently injected directly into the uterine muscle for this purpose after Cæsarian section.

2. *Vasopressin.* A striking effect of vasopressin is in **diabetes insipidus.** Injections, or insufflations of pituitary powder, in doses sufficiently high to produce evacuation of the bowel, relieve the thirst and control the diuresis. The stimulant effect on the smooth muscle of the intestine is made use of in **paralytic ileus,** where an immediate action of the bowel may follow the injection of ½ to 1 c.c. It is sometimes used as a **hæmostatic,** and may be of value as such in the operation of prostatectomy especially when performed by the transurethral route. It may be employed in cases of **circulatory failure** where its vaso-constrictor effect helps to restore the blood pressure. Posterior lobe extract directly antagonizes the action of insulin and may therefore be used in **hypoglycæmic coma.**

ANTERIOR PITUITARY EXTRACTS

Pituitary (Anterior Lobe) Extract (B.P.C.). An extract of the entire anterior lobe without differentiation of the separate active principles.

Gonadotrophic Extracts

From the anterior pituitary

Tr. Names. Ambinon B (Gonadotrophic and thyrotrophic); Gonadotraphon.

Dose, 50—200 M.U.—by injection.

From pregnancy urine

Tr. Names. Antoxylin-S; Antuitrin-S; Glanduantin Gonadotraphon-S; Gonan; Physostab; Pregnyl; Prolan.

Chorionic gonadotrophin from urine of pregnant women.

Dose, 100—2000 I.U.—by injection.

From the anterior pituitary and pregnancy urine

Gonadotrophinum Chorionicum (B.P.). Chorionic gonadotrophin is a sterile preparation from the urine of pregnant women. *Tr. Names.* Ambinon A; Synapoidin.

Dose, 100—500 units—by intramuscular injection.

Preparation (**B.P.**)

Injectio Gonadotrophini Chorionici
Dose, as above.

From pregnant mares' serum

Gonadotrophinum Sericum (B.P.). Serum gonadotrophin is obtained from the serum of pregnant mares. *Tr. Names.* Antostab; Gestyl; Luteoantin; Serogan.

Dose, 200—1000 units—by intramuscular injection.

Preparation (**B.P.**)

Injectio Gonadotrophini Serici.
Dose, as above.

Growth Hormone Extracts

Tr. Names. Antuitrin-growth; Crescormone; Krescone.

Dose, 1—5 ml.—by injection.

Thyrotrophic Hormone Extracts

Tr. Names. Thyrogan; Thyrotropin.

Dose, 50—100 guinea-pig units—by injection.

Lactogenic Hormone Extracts

Tr. Names. Physolactin; Prolactin.

Dose, 60—100 Riddle units—by injection.

Action

Gonadotrophic. The principle found in the serum of pregnant mares is mainly responsible for the growth and development of the ovarian follicle which secretes the œstrogenic hormone. In the male it controls spermatogenesis. The hormone present in pregnancy urine extracts controls corpus luteum formation and in the male ensures the development of the interstitial cells of the testis and the structures associated with its natural descent into the scrotum. There is little evidence that administration of chorionic gonadotrophin exerts any effect on the adult human ovary, though injection of serum, either in sequence or in combination with chorionic, gonadotrophin has been said to induce ovulation. Constantly repeated injections of serum gonadotrophin may lead to development of anti-gonadotrophic factors which may antagonize the effect of further administration of the extract.

Growth. Acromegaly and gigantism are known to be due to excessive secretion of the natural pituitary growth hormone which has now been isolated in pure crystalloid form.

Thyrotrophic. Administration of thyrotrophic hormone may lead not only to histological evidence of increased thyroid activity, but also to signs usually associated with Graves' disease, such as exophthalmos, and excess of thyrotrophic activity is believed to be the cause of exophthalmic goitre.

Adrenocorticotrophic. An adrenocorticotrophic hormone has recently been isolated in pure form. It stimulates enlargements of the adrenal cortex and discharge of its hormones with depletion of lipoids and ascorbic acid.

Lactation. The lactogenic hormone of the anterior pituitary is the factor responsible for milk secretion in a suitably prepared mammary gland such as exists at the end of pregnancy. Lactogenic extracts can increase the flow of milk in experimental animals and in the human female in whom this function is failing.

Other effects. There is some evidence that the anterior pituitary elaborates hormones which stimulate other endocrines, *e.g.*, the parathyroids, but extracts are not yet available for clinical use.

Therapeutics

Results obtained by the use of anterior pituitary extracts are on the whole disappointing. Disorders of menstruation due to inadequate pituitary stimulation of the ovary or abnormal resistance of the ovary to pituitary stimulation, and characterized by anovular cycles with amenorrhœa, oligomenorrhœa or excessive and irregular bleeding should theoretically respond to gonadotrophic extracts. Chorionic gonadotrophin alone seems to be ineffective, though it is sometimes employed in cases of excessive uterine bleeding. Courses of serum gonadotrophin followed by chorionic gonadotrophin represent a more rational form of treatment, though in doses at present employed they seldom succeed in regulating the menstrual cycle. It is possible that if they were given in much higher doses (3,000 units of serum gonadotrophin and 1,500 units of chorionic gonadotrophin) they might prove more effective, though the danger of over-stimulation of the ovary would not be absent. It has been stated that a pituitary synergist renders the ovary more responsive to stimulation but the clinical reports of the use of this type of preparation still require confirmation. Serum gonadotrophin stimulates spermatogenesis in immature animals, but the results obtained in cases of defective spermatogenesis in the human male have so far been disappointing. Again, this may be due to insufficient dosage or ineffective absorption from intramuscular injection. Some cases of adolescent pituitary obesity and hypogonadism seem to respond satisfactorily to chorionic gonadotrophin or to potent gonadotrophin preparations of the anterior pituitary. Probably the most satisfactory results are obtained in selected cases of **undescended testicle.** Where the testicle is mechanically obstructed from descending, surgery is the only remedy. In other cases spontaneous descent may take place at any time up to the age of fourteen or fifteen. It is, however, unwise to delay treatment beyond the age of nine to twelve owing to the possibility of incomplete development of spermatogenesis, and in more than 50 per cent. of the cases in which the testicle is unobstructed in the canal or outside the external ring treatment with injections of 500 units of chorionic gonadotrophin twice weekly results in descent to the scrotum in one to six months. In cases in which the position of the testicle is doubtful pre-operative trial of gonadotrophic therapy may be prudent, and in other cases where an incompletely developed testicle has been brought down by surgical means post-operative gonadotrophic therapy is a wise form of after-treatment.

Little progress has been made in the clinical use of growth and lactogenic extracts and there seems to be little indication for thyrotrophic hormone while extracts of the thyroid gland itself continue to provide complete substitution in cases of hypothyroidism. Adrenocorticotrophic hormone is not generally available for clinical use, though it has been employed experimentally in cases of adrenal cortical deficiency. It is not yet established that such treatment is more effective than administration of the available cortical hormones.

OVARY

Œstrogens

Œstrogens are available as chemically pure compounds. Those employed are either " natural œstrogens " extracted from sources such as pregnancy urine, or " synthetic œstrogens " exemplified by the stilbene group, which are prepared in the laboratory and are relatively simple chemical substances.

Natural Œstrogens

There are three natural œstrogens, œstrone, œstriol and œstradiol. Œstradiol is the true active principle of the ovarian follicle, and is considerably more potent as œstrone by the intramuscular route. It is therefore the " natural " œstrogen chosen for injection. Its activity is prolonged by esterification and it is injected either in the form of œstradiol benzoate or dipropionate, the effect of a single injection lasting for at least three days, so that twice weekly injections are commonly employed. Œstrone is the preparation commonly employed in this country for oral administration.

Œstronum (B.P.). $C_{18}H_{22}O_2$. $\triangle^{1.3.5.}$ œstratriene-3-ol-17-one.

Synonym. Ketohydroxyœstrin. *Tr. Names.* Glandubolin; Ketodestrin; Kolpon (vaginal tablets); Menformon; Œstrin; Œstrosalve (ointment); Ovostab; Progynon; Solestrin (alcoholic solution); Theelin; Unden.

A pure crystalline excretion product of the ovarian follicular hormone œstradiol, extracted from pregnancy urine.

Dose, $\frac{1}{60}$—$\frac{1}{6}$ gr. 1—10 mg.

Preparation (**B.P.**)

Tabellæ Œstroni. Contains 1 mg. in each.
1 mg. Œstrone contains 10,000 units.

Œstradiol. $C_{18}H_{24}O_2$. $\triangle^{1.3.5.}$ œstratriene-3-17-diol.

Tr. Names. Benztrone; Œstroform; Ovocyclin; Progynon (ointment).

This, the true hormone of the ovarian follicle, is prepared by the hydrogenation of œstrone extracted from urine of pregnancy.

Dose, 1000—50,000 I.B.U. (0·145 mgm.)—by mouth and by injection.
1000 I.B.U. (0·1 mgm.) per gm.—ointment.

Œstradiolis Monobenzoas (B.P.). *Synonyms.* Dihydroxyœstrin monobenzoate, Estradiol benzoate.

Tr. Names. Dimenformon; Œstrin; Progynon B. Oleosum; Unden.

Dose, $\frac{1}{60}$—$\frac{1}{12}$ gr. 1—5 mg.—by intramuscular injection.

Preparation (**B.P.**)

Injectio Œstradiolis Monobenzoatis. Contains 1 mg. ($\frac{1}{60}$ gr.) in 1 ml. (15 min.).

Dose, $\frac{1}{60}$—$\frac{1}{12}$ gr. 1—5 mg.

Œstradiol Dipropionas (B.P.).

Tr. Names. Dimenformon Dipropionate; Ovocyclin P.

Dose, $\frac{1}{60}$—$\frac{1}{12}$ gr. 1—5 mg.—by intramuscular injection.

Preparation (**B.P.**)

Injectio Œstradiolis Dipropionatis. Contains 1 mg. ($\frac{1}{60}$ gr.) in 1 ml. (15 min.).

Dose, $\frac{1}{60}$—$\frac{1}{12}$ gr. 1—5 mg.

Synthetic Œstrogens

The chief characteristic of the synthetic œstrogens is their oral potency. Stilbœstrol given by mouth is roughly comparable in œstrogenic effect to the corresponding dose of a natural œstrogen by injection. It is certainly considerably more potent than œstrone given by mouth. It is also much cheaper, but it possesses the disadvantage that it produces mild toxic effects, such as nausea, headache and depression in about 20 per cent. of cases. These toxic effects occur more frequently when high doses are given and are usually transient and disappear if treatment is continued. Toxic effects of synthetic œstrogens are never seen in pregnant or puerperal women, in children, and seldom in men. Hexœstrol appears to be less likely to produce toxic effects than stilbœstrol, though clinically it seems to be considerably less potent in corresponding doses.

Dienœstrol is about three times less potent than stilbœstrol though it appears to be specifically less toxic than stilbœstrol.

Stilbœstrol (**B.P.**). $C_{18}H_{20}O_2$ 4 : 4′-di-hydroxy-$\alpha\beta$-diethylstilbene.

Synonym. Diethylstilbœstrol.

Tr. Names. Clinestrol, Neo-œstranol-I; Ovendosyn; Pabestrol.

Dose, $\frac{1}{120}$—$\frac{1}{30}$ gr. 0·5—2 mg.

Preparations are made up in doses of 0·1 to 5 mgms.—by mouth and by injection. 1 mgm. per gm.—ointment.

Preparation (**B.P.**)

Tabellæ Stilbœstrolis. Contain $\frac{1}{130}$ gr.—0·0005 grm. in each.

Stilbœstrol dipropionate.

Tr. Names. Clinestrol Neo-œstranol-II; Pabestrol D; Syntestrin.

Dose, 0·1—5 mg.—by mouth and by injection.

Hexœstrol (**B.P.**). $C_{18}H_{22}O_2$. *Tr. Name.* Synthovo.

Dose, $\frac{1}{60}$—$\frac{1}{12}$ gr. 1—5 mg.

Preparation (**B.P.**)

Tabellæ Hexœstrolis. Each tablet contains 1 mg. ($\frac{1}{60}$ gr.).

Dienœstrol (**B.P.**). $C_{18}H_{18}O_2$.

Dose, $\frac{1}{600}$—$\frac{1}{12}$ gr. 0·1—5 mg.

Preparation (**B.P.**)

Tabellæ Dienœstrolis. Each contains $\frac{1}{600}$ gr.—0·1 mg.

Action

It would appear that the tissues and systems of the organism vary in the extent to which they respond to œstrogens; some tissues, such as the vaginal epithelium, the uterine endometrium and the mammary gland are relatively œstrogen-sensitive; others, such as the skin, the skeletal muscles and the blood vessels are relatively œstrogen-resistant. In the normal individual the œstrogen-sensitive tissues are already adequately supplied with œstrogens derived from such natural sources as the actively functioning ovarian follicle, and any additional œstrogen which may be administered exogenously is metabolised and excreted in relatively inactive form without producing any obvious physiological action. Sufficiently high doses administered continuously for adequate periods, however, may lead to recognizable changes, such as painful **swelling of the breasts,** both in the female and, more particularly, in the male. Such administration, furthermore, may lead to a persistence of the integrity of the uterine endometrium and so may **delay the onset of menstrual bleeding.** It may even be possible to inhibit to some extent the activity of the anterior pituitary, and this is best exemplified by **prevention of engorgement of the breasts** which occurs when œstrogens are administered in sufficient quantities when breast feeding is contraindicated. Where there is evidence of relatively mild or recent deficiency of ovarian activity, such as occurs in the early days of the climacteric, the œstrogen-sensitive tissues respond spectacularly to comparatively low doses of œstrogen. Finally, if complete absence of œstrogen secretion has persisted for some time, or if for any other reason the normally œstrogen-sensitive tissues have become resistant and atrophic, then only the most concentrated exhibition of high doses is capable of reversing the condition. Thus, though it is difficult to influence the normal or completely atrophic tissue by œstrogenic administration, satisfactory results are obtained from œstrogenic therapy of œstrogen-sensitive tissues incompletely or recently deprived of their normal œstrogenic stimulus.

Therapeutics

The most satisfactory response to œstrogenic therapy is seen in the **menopausal syndrome.** Relatively small doses such as 0·1 mgm. to 1 mgm. of stilbœstrol, given daily by mouth control the hot flushes, headaches, giddiness, lack of concentration, depression, &c. Some of the later results of the climacteric ovarian deficiency require higher doses, such as 1 to 3 mgm. daily, but respond equally satisfactorily. This is especially true of the **climacteric disorders of the vagina and vulva,** such as pruritus, kraurosis and atrophic vulvitis and senile vaginitis and ulceration. Certain of the psychological manifestations of the climacteric, such as **involutional melancholia,** may respond to similar treatment. Some success has been achieved in the treatment of certain **dermatological disturbances in elderly women,** particularly those associated with hyperkeratosis. **Migraine** appearing in the premenstrual week or occurring after the menopause is sometimes relieved by œstrogens. **Hypertension** may become evident at the menopause and is said to be relieved in cases in which there are signs of general improvement as the result of œstrogen administration. A type of **arthritis** associated with hypertrophy of the synovial tissues occurring in obese subjects is said to be characteristic of the menopause and to respond favourably to œstrogens. Œstrogens are employed in the treatment of menstrual disorder. In cases of **amenorrhœa** even of long-standing it is usually possible to induce uterine hæmorrhage following a course of œstrogen injections, but this is not the first sign of re-establishment of the menstrual rhythm, but rather a single withdrawal bleeding which will not be repeated unless another course of œstrogenic therapy is given. In milder types, such as hypomenorrhœa and oligomenorrhœa, or in amenorrhœa of relatively recent onset, normal rhythm and loss may sometimes be re-established by œstrogenic therapy, the effect being produced probably by rendering the endometrium less resistant and therefore capable of responding cyclically to the secretions of the patient's own ovaries. Œstrogens have been shown to have a *hæmostatic* effect due probably to constriction of the endometrial vessels. Large doses of stilbœstrol up to 20 mgm. in a day will stop uterine hæmorrhage within twenty-four hours. This treatment, which will almost certainly give rise to such toxic symptoms as vomiting, should only be employed where the need to arrest flooding is urgent. In some species œstrogen increases the spontaneous activity of the uterine muscle and renders it more sensitive to the action of oxytocin. It seems capable also of regulating the tone of human uterine muscle, and may assist in the treatment of **uterine inertia,** or in the expulsion of a **missed abortion.** It also relieves some cases of **dysmenorrhœa** when given in appropriate doses preferably during the first half of the menstrual cycle. Œstrogens are responsible for the growth of the **mammary gland** and may be given in cases where the breasts are undersized, being particularly effective by ununction. It has already been mentioned that œstrogens may inhibit the activity of the pituitary, and that use is made of this to **prevent puerperal engorgement of the breasts** in the absence of suckling by inhibiting the secretion of the pituitary lactogenic hormone. Attempts have also been made to cause pituitary inhibition in certain clinical manifestations of its over-activity such as **Cushing's syndrome, acromegaly** and **Graves' disease,** but with little more than temporary success in the first condition only.

The use of œstrogens has recently been extended to the male. It has been shown that in **carcinoma of the prostate** œstrogens, given in most cases in the form of stilbœstrol, result in clinical disappearance of the growth and of the X-ray evidence of the bony metastases, as well as in the most remarkable alleviation of symptoms. It is too early to say that this amelioration of signs and symptoms is permanent. In **acne,** which has been shown to be a manifestation of excessive androgenic activity, the administration of large doses of œstrogen such as implantation of two 100 mgm. pellets for three or four months has led to a degree of "œstrogenization" which though accompanied by such temporary manifestations as gynæcomastia completely inhibits the active stage of the condition during the therapeutic period. Such treatment, however, should be employed only in carefully selected cases and with extreme caution, especially in the male, for it may give rise to impotence, testicular atrophy and defective spermatogenesis.

CORPUS LUTEUM HORMONE

Progesteronum (B.P.). Progesterone. *Synonym.* Progestin. $C_{21}H_{30}O_2$. Pregnene-3·20-dione. 1 mg. contains 1 unit.

Tr. Names. Gestone; Glanducorpin; Lipo-Lutin; Luteostab; Lutocyclin; Progestin; Proluton.

Source. A solution in oil of the pure crystalline material prepared either by extraction of the corpora lutea of sows or by synthesis from stigmasterol, a constituent of the soya bean. The synthetic material is more usually employed.

Dose, $\frac{1}{30}$—$\frac{1}{3}$ **gr.** **2—20 mg.**—by intramuscular injection.

Preparation (B.P.)

Injectio Progesteroni. Contains 5 mg. ($\frac{1}{12}$ gr.) in 1 ml. (15 min.).

Dose, $\frac{1}{30}$—$\frac{1}{3}$ **gr.** **2—20 mg.**—by intramuscular injection.

Action

Progesterone has no effect on any tissue which has not been previously primed by œstrogen. It will, however, transform an endometrium in the full state of proliferation characteristic of œstrogenic stimulation into the progestational condition which is essential for the nidation of the fertilized ovum. It is responsible for the further development of the epithelial elements of the ducts and alveoli of the mammary gland initiated by œstrogen, and prepares the breast for lactation which occurs on the release of the pituitary lactogenic hormone, prolactin.

Therapeutics

Progesterone is employed in the treatment of **threatened** and **habitual abortion.** Chemical urinary analysis of its excretion product pregnanediol has shown that abnormally low values may be found in these conditions. Intensive treatment in doses up to 20 mgm. daily is desirable where the abortion is already threatened, whereas in cases giving a history of at least two, and preferably at least three, previous early miscarriages the administration of progesterone in doses of 5 mgm. on alternate days up to the sixteenth week of pregnancy or by implantation of six 25 mgm. pellets has coincided with the pregnancy being carried to term in about 70 per cent., though some authorities believe that such a satisfactory outcome would have been attained without treatment. Progesterone has been used successfully in the treatment of *excessive and irregular bleeding.* Once a bout of flooding has been controlled, *e.g.* by œstrogen as indicated above, or has ceased spontaneously, the administration of 10 mgm. of progesterone given every other day for four doses at twenty-eight day intervals will usually induce artificial cycles in which the bleeding, generally normal in amount, occurs two or three days after the last injection of the course. Daily administration during the third week of the menstrual cycle has been suggested in cases of **sterility** thought to be due to failure of nidation.

Ethisterone

Æthisteronum (B.P.) (Pregneninolone; anhydroxy-progesterone; ethinyl testosterone). $C_{21}H_{28}O_2$. 17-ethinyl-Δ-4-pregnenine-17-ol-3-one.

Tr. Name. Gestone-oral; Progestoral; Proluton C.

Dose, $\frac{1}{12}$—$\frac{2}{5}$ gr. 5—25 mg.—by mouth.

Preparation (**B.P.**)

Tabellæ Æthisteroni. Contains $\frac{1}{12}$ gr. (5 mg.).

Action

The action is qualitatively similar to that of progesterone. It is said to be about one-sixth as active by mouth as progesterone is by injection.

Therapeutics

The orally active compound may be employed in case of habitual abortion or menorrhagia. Its effectiveness, however, is variable and though the usual dose is 30 mgm. a day, in some cases such large doses as 200 mgm. daily are not completely successful. Ethisterone is usually employed where injections of progesterone are found to be irksome. It is used during the premenstrual week in cases in which there is evidence of deficient luteinization, and also in some cases of so-called *premenstrual tension* in which the symptoms of fullness, headache and mental distress are thought to be due to unopposed action of œstrogen in the last half of the menstrual cycle.

Toxicity

Nausea and vomiting may be experienced, particularly when the dosage is high.

TESTIS

Androgens

Testosterone (**B.P.C.**). $C_{19}H_{28}O_2$-$\triangle^4$-androstene-17-ol-3-one.
Tr. Names. Neohombreol (suppositories); Testoviron ointment.

The true testicular hormone prepared synthetically by degradation of cholesterol.

Dose, 2 mg. per G.—ointment.

Testosteroni Propionas (**B.P.**). $C_{22}C_{32}O_3$.
Tr. Names. Neohombreol; Perandren; Testoviron; Virormone.

Dose, $\frac{1}{12}$—$\frac{2}{5}$ gr. 5—25 mg.—by intramuscular injection.
2 and 25 mg. per G.—ointment (*not* **B.P.**).

Preparation (**B.P.**)

Injectio Testosteroni Propionatis. Contains 10 mg. ($\frac{1}{6}$ gr.) in 1 ml. (15 min.).

Dose, as for Testosterone Propionate.

Methyltestosteronum (**B.P.**). $C_{20}H_{30}O_2$.
Tr. Names. Neohombreol (M); Perandren; Virormone—oral.

An androgenic compound active by mouth.

Dose, $\frac{2}{5}$—$\frac{3}{4}$ gr. ($\frac{1}{12}$—$\frac{1}{3}$ gr. in women) 25—50 mg. (5—20 mg. in women).

Preparation (**B.P.**)

Tabellæ Methyltestosteroni. 5 mg. in each.

Action

Androgens affect not only the male but also the female organism. In the male they are responsible for the development of the male secondary sex characters. They are certainly responsible for the sex urge in the male and possibly also in the female. In women they neutralize many of the effects of œstrogen. For instance, they lead to the appearance of a " menopausal " type of vaginal smear, they render the endometrium atrophic, and may arrest the menstrual rhythm and give rise to amenorrhœa. Given in large doses they produce certain masculinizing effects such as deepening of the voice, growth of hair on the upper lip and chin, and enlargement of the clitoris.

Therapeutics

Androgens are chiefly employed as replacement therapy for conditions of male hypogonadism due to delayed sexual development, or injury or disease of the testis. Adequate though temporary replacement of function is obtained in the male castrate or in the condition of **enuchoidism,** with enlargement of the penis and erections, growth of pubic and facial hair and deepening of the voice. Androgenic therapy has also been advocated for male **impotence,** but in the absence of obvious physical evidence of testicular deficiency any beneficial effect it may have is probably entirely psychological.

In the female, androgens are effective in controlling the excessive hæmorrhage in certain cases of **menorrhagia** and relieve **dysmenorrhœa.** They may also allay the symptoms of mastodynia and **chronic mastitis.**

CLASS B

PANCREAS

Insulinum (B.P.). Source. A preparation containing the specific, anti-diabetic principle of the mammalian pancreas (fresh, or frozen). The pancreas is finely divided and subjected to repeated treatment with 95 per cent. alcohol, filtration and evaporation. The active material is dried and powdered. The pharmacopœia gives instructions for its preparation in solution and in tablet form.

Characters. Colourless, clear liquid which must comply with tests for sterility. The potency is determined by biological assay and expressed in units per millilitre.

Dose—by injection. The dose is determined by the physician. Twenty units per mil. shall be dispensed unless otherwise specified.

Unit. This is the activity of $\frac{1}{22}$ mgm. of standard crystalline insulin.

Action

Insulin is essential to the storage and use of carbohydrates by the tissues. When a healthy animal or man receives a dose of insulin, the sugar in the blood quickly diminishes from the normal of 0·12 per cent., and, if the dose has been sufficiently large, symptoms of hypoglycæmia supervene, viz. confusion, hilarity, or aggressiveness ; weakness, faintness, pallor, sweating, palpitation, incoordination, failure of sight, depression of nervous reflexes and coma. A fall of blood-sugar produces sympathetic stimulation and increased adrenaline release to which some of the symptoms of insulin overdosage are attributable. In man symptoms occur when the blood sugar has fallen to 0·06 or 0·05 per cent. They are promptly relieved by the administration of glucose by mouth or stomach-tube (50 grm.), or intravenously (20 grm. in 40 mils), or of ordinary lump sugar in mild cases. Liq. Adrenalin (0·5 mil) may be injected. The action of the drug is dependent upon an adequate supply of glycogen in the liver which it causes to be converted to glucose. Ten units of insulin injected intravenously produce, in twelve to fifteen minutes, waves of powerful gastric peristalsis occurring in groups and separated by quiescent periods similar to those which arise as the result of fasting. The effect is seen when the blood sugar falls to 0·08 per cent. or lower and can be abolished by the administration of atropine or of sugar. The acidity of the gastric juice is also increased by insulin.

Therapeutics

Insulin is of great use in **diabetes,** causing a rapid fall in the amount of blood sugar. The sugar, acetone and acetoacetic acid in the urine rapidly decrease, lipæmia disappears, the symptoms of acidosis pass away, and the patient is able to take and utilize more food, including carbohydrates ; hence he gains weight. Surgical operations which could not otherwise be undertaken can be performed with safety if the diabetic is under the influence of insulin.

Insulin is useless by the mouth. It is given subcutaneously as an aqueous solution. The usual initial dose for an adult is 10 to 15 units about a quarter of an hour before a meal, so that it will be able to exert its effect on the glucose which reaches the blood from the meal. Usually at least two doses a day are necessary, but the one in the evening should be smaller than that in the morning lest the insulin acting during the abstinence from food during the night should, reducing the sugar of the blood too much, produce the dangerous symptoms of hypoglycæmia. If these occur they can be abolished by half an ounce of glucose or other sugar, in water, orally ; or, if the patient is comatose, the sugar may be given by stomach tube or as a 50 per cent. solution intravenously.

Coma is overcome by the administration of insulin and glucose. The value of the latter is that it enables the liver to replace its depleted store of glycogen and also, under the influence of insulin, the sugar is metabolized with consequent disappearance of acidosis. Usually such therapy starts with the giving of 40 units of insulin and 40 grms. of glucose.

Insulin is not curative of diabetes, although some cases do eventually recover under its use so that it may be abandoned. To begin with, at any rate, it must not be given without determinations of the blood sugar, for some patients with glycosuria are not suffering from diabetes ; and in diabetes innocens, in which the glycosuria is due to abnormal permeability of the renal cells for glucose, the blood sugar is always low and insulin easily causes dangerous hypoglycæmia. Further, in an ordinary case of diabetes, estimations of the blood sugar at frequent intervals enable us to see the effect of the insulin and to arrive at its appropriate dose.

Protamine Insulinate is a compound of insulin with such protamines as scombrine, salmine, and salmiridin. It is used because of its slower absorption after injection. The action of insulin is thus spread out more evenly, the danger of hypoglycæmia being diminished. The delayed effect is actually produced by the addition of a buffer solution containing sodium phosphate to produce *Insulin retard.*

Injectio Insulini Protaminati cum Zinco (B.P.). *Synonym.* Protamine Zinc Insulin.

Dose—by injection. The dose is determined by the physician. Forty units per ml. shall be dispensed unless otherwise specified.

Zinc-Protamine-Insulin possesses this property to a still greater degree. Whereas ordinary insulin begins to act in 30 minutes with its maximum effect in 3 hours, the corresponding figures for insulin retard are 3 and 8 hours ; for zinc protamine insulin, 10 and 20 hours. With large doses the maximum effect of the zinc preparation may even be seen 30 hours after injection. Zinc protamine insulin is far less stable than the other two preparations and tends to lose potency in a few months. A single injection of the zinc preparation will usually replace two or three daily injections of insulin, but in order to avoid hyperglycæmia during the first part of the day it is usually necessary to give a small dose of ordinary insulin. The two forms of insulin should not be mixed in the syringe because the Z.P.I. may precipitate the soluble insulin. The latter is given first and the needle is left in place. A syringe containing Z.P.I. is then attached to the needle and the injection completed.

The combined injection is as a rule given before breakfast. If hypoglycæmia should develop, however, it will be more persistent after the zinc insulin suspension.

Globin Insulin. This is a compound of 1000 units insulin, 38 mgm. globin, and 3 mgm. zinc chloride.

The advantage claimed for it is that its effect develops nearly as quickly and as powerfully as that of ordinary insulin and that it acts twice as long. On the other hand it does not have such a delayed and prolonged action as Z.P.I., consequently there is less danger of its producing hypoglycæmia in the night. Globin insulin produces a fall in blood-sugar within 2 hours of injection and is thus intermediate between soluble insulin (S.I.) and Z.P.I. The duration of action is from 12 to 16 hours.

LIVER

1. Extractum Hepatis Liquidum (B.P.).

Source. A fraction of an alcoholic extract of ox or sheep liver, dissolved in glycerin, alcohol and distilled water. *Strength:* One fl. oz. contains the equivalent of 8 ozs. of fresh liver.

Dose, 1 fl. oz.—30 ml.

STOMACH

Ventriculus Desiccatus (B.P.C.). *Tr. Name.* Ventriculin.

The desiccated wall of a healthy pig's stomach.

Characters. A greyish-white powder of unpleasant odour insoluble in water.

Dose, $\frac{1}{4}$—1 oz. 8—30 G.

Liver and extract of liver have a powerful action in restoring the blood to a normal condition in cases of pernicious (Addison's) anæmia. Before this was discovered, the disease was invariably fatal, and reliance was placed upon repeated blood transfusions and the exhibition of large doses of arsenic to prolong life. The latter drug probably acted beneficially by damaging the patient's liver and thus releasing some of the essential substance into the blood stream. Concentrated extracts in powder, or liquid, form are available for administration by mouth, and highly concentrated liquid preparations can be given intramuscularly, or even intravenously. This has overcome the initial difficulty of the nausea produced by the patient's having to take half to one pound of lightly cooked liver daily. The best extracts may be injected in doses of 1 c.c. weekly until the blood is normal and, thereafter, a maintenance dose of 1 c.c. once in two to four weeks is adequate. A highly purified concentrate of liver is called *Anahæmin.* It was shown later that dried pig stomach produced equally good results as liver, and, in fact, 1 oz. of such a preparation was approximately equal in efficacy to ½ lb. of liver. These facts and the demonstration that pernicious anæmia could be benefited by the administration of meat which has undergone partial digestion in a normal stomach led to the belief that two active principles are concerned. The first, known as the **intrinsic factor,** is a hormone secreted in the gastric juice. The second, known as an **extrinsic factor,** is liberated by the digestion of meat in the stomach. Both of these factors are presumably contained in liver, and in stomach wall.

When liver, or stomach, is given to a patient with **pernicious anæmia,** the first effect which is seen in the blood is an increase in reticulocytes which usually occurs in about four or five days, reaches a maximum about the ninth day, and then declines to reach normal again by the end of the third week. This so-called *reticulocyte crisis* may show a rise of the reticulocyte count from 4 per cent. or less up to 35 per cent. The lower the initial red cell count the higher will be the reticulocyte rise. As the reticulocytes diminish, so the normal red cells increase, as also the hæmoglobin. The colour index rapidly returns to below unity. Within a few weeks the blood count is normal, except that the hæmoglobin is still usually depressed somewhat, unless iron is given as well. This is most likely to be noticeable when concentrated liver extract or stomach is given, because neither of these contain iron. It is of interest to note that given adequate amounts of liver all cases will recover in approximately the same time, viz. two months, even although the initial erythrocyte counts may differ by two million or more. The signs of sub-acute combined degeneration of the cord, if present, may become less, but those due to actual destructive lesions in the central nervous system will not recede. An important point to be borne in mind is that if subsequent treatment with liver, or stomach, be below the optimum dosage, although the blood will not be sufficiently impoverished to give rise to symptoms, yet the nervous changes may progress. It is essential, therefore, for a blood examination to be made from time to time for the rest of the patient's life. No improvement is likely to occur in the condition of achylia which normally exists in pernicious anæmia. On the other hand, its correction by the administration of hydrochloric acid and pepsin has no effect upon the condition of the blood. Glossitis nausea and the rare abdominal pain of pernicious anæmia disappear under liver treatment. Other macrocytic anæmias, notably that in **sprue**, are greatly benefited by liver and stomach therapy.

It has been suggested that the active principle in liver and stomach is twofold; a moiety is necessary for the maturation of the red corpuscles (**hæmopoietin**), and a further fraction for the maintenance of the health of the spinal cord (**neuropoietin**). In addition, it has been recognized that in the presence of achylia the absorption of vitamin B_1 and of iron is frequently deficient. The former may lead to polyneuritis. The latter, as has been pointed out, may cause a persistence of iron deficiency anæmia once the pernicious anæmia has been overcome. In such cases both substances should be administered as well. Recent work has shown that the principle elaborated in the stomach is produced in the fundus and cardiac end over an area corresponding more or less to that of the distribution of oxyntic cells. In pernicious anæmia this portion of the stomach shows a general atrophy involving all coats, and there is not as a rule any evidence of a preceding inflammatory lesion.

GROUP XXIX

Ephedrine and Amphetamine

EPHEDRINE

Ephedrina (B.P.). An alkaloid obtained from *Ephedra sinica* and other species of *Ephedra*. It is closely related chemically and pharmacologically to adrenaline.

Ephedrinæ Hydrochloridum (B.P.). The hydrochloride of the alkaloid ephedrine.

CHARACTERS. Ephedrine hydrochloride occurs as white prismatic crystals; soluble in water and alcohol; very stable; can be boiled. Solutions lævorotatory.

Dose, ¼—1½ gr. 16—60 mg.

Preparation (B.P.)

Tabellæ Ephedrinæ Hydrochloridi. Contain ½ gr.—0·03 G. in each.

Pseudo-ephedrine is the dextrorotatory optical isomer of ephedrine and is half as powerful in action.

Action

External. Applied to mucous membranes or denuded surfaces it causes blanching by vaso-constriction.

Internal. Ephedrine exerts a stimulating action on the cerebral cortex. It appears thus to relieve fatigue and to produce insomnia. Its peripheral action is similar to that of adrenaline. It differs from this drug, however, in that it produces remote effects when given by mouth.

Furthermore, it is more stable, its action is more prolonged and its effect diminishes if given repeatedly. Another point of difference is that section of certain sympathetic adrenergic nerves followed by degeneration increases the effect of adrenaline, but diminishes that of ephedrine. In fact, its action is in some way similar to that of physostigmine on the cholinergic nerves and is exerted by potentiating the action of adrenaline by protecting it from destruction at the adrenergic nerve endings.

In certain individuals it gives rise to unpleasant symptoms, viz. palpitation, headache, insomnia. and retention of urine; the last-named particularly in children. In therapeutic doses it stimulates the terminations of the sympathetic system causing a rise of blood pressure, mydriasis, tachycardia and relaxation of bronchial spasm if present.

Therapeutics

Used in **asthma** with considerable success: relief is experienced in about twenty minutes after administration per os. It also reduces the dyspnœa of **emphysema** presumably by inducing relaxation of bronchioles. Occasionally used locally as a **mydriatic** (4 per cent.), and in the form of a nasal spray for **hay fever.** If taken early in an attack it may abort **migraine.** It has also been used in full doses in the treatment of **narcolepsy** because of the insomnia which it is apt to produce. Taken at bedtime it is of great value in the treatment of **enuresis nocturna.** It is also useful in the treatment of **myasthenia gravis,** although its precise mode of action is not yet understood.

AMPHETAMINE

Amphetamina (B.P.). *Tr. Name.* Benzedrine.

CHARACTERS. Colourless slowly volatile liquid, soluble in alcohol, ether, and acids.

Amphetaminæ Sulphas (B.P.). *Tr. Name.* Benzedrine sulphate.

Amphetamine sulphate is a synthetic product which is β-aminopropylbenzene sulphate.

CHARACTERS. White odourless powder ; bitter taste followed by numbness. Soluble in water.

Dose, $\frac{1}{24}$—$\frac{1}{6}$ gr. 2·5—10 mg.

Action

Applied to mucous membranes it causes contraction of the blood-vessels and shrinkage of the membrane. Its vapour has been inhaled to free the congested nasal passages in coryza.

Taken by mouth in the form of the sulphate it resembles in many ways ephedrine. A dose of 40 mg. raises the blood pressure. The effect is seen in one to two hours after administration, reaches its maximum one hour later, and passes off completely in two to five hours after the peak has been attained. The systolic pressure is chiefly affected, and rises from 20 to 40 mm. Hg.

It diminishes to a slight extent the activity of the gastrointestinal tract, but increases the gastric secretion of acid and pepsin. It tends to abolish fatigue especially in depressed patients in whom it may induce elation. Palpitation, tremor, anginal pain, hallucinations, aggressiveness, skin rashes, and aplastic anæmia have been described as resulting from the use of the drug. Sleeplessness may follow a moderate dose many hours after its administration.

Therapeutics

Amphetamine sulphate is used for **narcolepsy, post-encephalitic parkinsonism,** depressive psychoses, arterial hypotension, spasmodic conditions of the digestive tract and spasmodic torticollis.

The drug must not be used in cases of hypertension or other cardiovascular disease. Precordial pain and even collapse has been induced by it in apparently healthy persons.

GROUP XXX

Antitoxic Sera and Toxins

Antibodies which neutralize toxins are called antitoxins, and are the active principles of antitoxic sera. They are prepared from the blood of animals which have been immunized by graded injections of sterile filtrates from cultures of the specific organism. Their administration, if sufficiently early in the disease, will neutralize much of the circulating poison, and may produce dramatic improvement. No permanent immunity is thus caused. It is referred to as passive immunity. To prevent certain diseases, on the other hand, active immunity is called forth by the administration of minute quantities of the actual toxin. The body then forms its own antitoxins and appears to retain this power for many years, thus deriving more or less permanent immunity.

Serum Sickness

Poisoning symptoms are sometimes seen after any antitoxic serum has been given, but they are rarely severe. They are not due to the antitoxin, but to some other constituent of the serum, for they may follow when the simple serum of animals is injected into the human subject. The most common is a rash, associated with intense itching, met with in about 35 per cent. of the patients injected ; it may appear as late as the end of the third week after injection, but it is usually seen at the end of the first week. It often recurs for a week or so. It may be mere erythema, but is often urticarial. Commonly it disappears in three days. Pain and swelling of the joints are occasionally present, and may be associated with pyrexia. It is said that they may often be benefited by the administration of ephedrine and 10 per cent. calcium chloride (10 mils) intravenously.

True anaphylaxis seldom arises in man unless the initial and the evocative doses be given intravenously.

DIPHTHERIA ANTITOXIN

Antitoxinum Diphthericum (B.P.). A serum, or a preparation from serum, containing the antitoxic globulins, which have the specific power of neutralizing the toxin formed by *Corynebacterium diphtheriæ.*

Strength. The potency is determined by biological assay and expressed in units. Liquid preparations contain not less than 500 units per ml., and solid preparations not less than 5000 units per gramme.

Dose, by injection—Prophylactic, 500—2000 units ; therapeutic, not less than 10,000 units.

Action and Therapeutics

Antitoxic serum diminishes the symptoms of diphtheria, and in particular it greatly lessens the liability to sudden cardiac failure. Both clinical and experimental evidence show that after antitoxin is given, although the bacilli continue to exist in the throat, the formation of membrane ceases and that which is present rapidly disappears ; therefore laryngeal diphtheria rarely follows faucial if antitoxin is used early, the patient becomes less anæmic, his pulse improves, and his temperature may fall a little, although this is less influenced by antitoxin than are the other symptoms of diphtheria. The maximum effect of the antitoxin is not seen till twenty-four hours after injection. All reliable collections of cases show that the mortality, especially in children, is much less when the antitoxin is used. It should be given at the earliest possible moment, even if it is only likely that the patient is suffering from diphtheria, for the number of fatal cases is less when antitoxin is used early in the illness. The benefit is more marked in laryngeal than in other varieties of diphtheria, the mortality of tracheotomy cases falling by one-half. The frequency of the occurrence of paralysis is not diminished, but the percentage of recoveries in cases with paralysis is slightly increased. When a case of diphtheria is discovered in a school, the other children who have been associated with the patient should be subjected to the Schick test, and if found sensitive should have 500 units given to each as a preventive. The protection conferred lasts about three weeks.

DIPHTHERIA PROPHYLACTIC

Toxinum Diphthericum Detoxicatum (B.P.). A sterile filtrate of a culture of *Corynebacterium diphtheriæ*, the specific toxicity being reduced to a low value. Strength determined by biological assay.

There are four official forms of Diphtheria Prophylactic :—

1. *Formol Toxoid or Anatoxin, i.e.* the filtrate of the culture treated with formaldehyde.
2. *Toxoid-Antitoxin Mixture, i.e.* toxin, formaldehyde and antitoxin.
3. *Toxoid-Antitoxin Floccules, i.e.* the floccules of toxoid and antitoxin suspended in saline.
4. *Alum Precipitated Toxoid, i.e.* formol toxoid and alum precipitate, which is separated and suspended.

Abbreviations : (1) = F.T. ; (2) = T.A.M. ; (3) = T.A.F. ; (4) = A.P.T.

Doses. By intramuscular injection :
F.T. Volume on label ; 4 weeks between 1st and 2nd dose ; 2 weeks before 3rd.
T.A.M. 3 doses of 1 ml. Intervals as for F.T.
T.A.F. The same as T.A.M.
A.P.T. 0·2—0·5 ml. ; after 4 weeks, 0·5 ml.

All these preparations confer active immunity which lasts for many years. A.P.T. is the best preparation for children, but it produces local reactions in adults for whom T.A.F. is to be preferred.

SCHICK TEST TOXIN

Toxinum Diphthericum Diagnosticum (B.P.). A sterile filtrate from a culture of *Corynebacterium diphtheriæ* diluted before use so that 0·2 ml. contains the Test Dose.

Dose, 3 min.—0·2 ml.—by intradermal injection.

SCHICK CONTROL

Toxinum Diphthericum Calefactum (B.P.). A Schick test toxin heated to a temperature of not less than 70° for five minutes. It must be prepared from the same batch of test toxin as that with which it will be used. It is employed as control of the Schick test, as the heating destroys the specific toxin. Any reaction due to non-specific bodies can thus be appreciated.

Dose, 3 min.—0·2 ml.—by intradermal injection.

Diphtheria toxin is used for the Schick test. Three minims of the Schick test toxin are injected into the skin of the palmar aspect of one arm and a like quantity of the Schick control into that of the other arm. The punctures are examined daily for three days. A positive reaction indicating susceptibility to diphtheria is shown by a raised wheal ½ to 1 inch in diameter on the test arm, whilst the control exhibits a trivial hyperæmia due to trauma only. If both arms develop a hyperæmic area with central darker red point a pseudo-reaction is diagnosed. It is due to susceptibility to some constituent other than the actual toxin. Protection is afforded by an injection of diphtheria toxin antitoxin mixture.

TETANUS ANTITOXIN

Antitoxinum Tetanicum (B.P.). *Strength.* Not less than 1000 units per ml., and 10,000 per G.

Dose, by injection; Prophylactic, not less tnan 3000 units; therapeutic, not less tnan 100,000 units.

This is prepared on the same principles as diphtheria antitoxin (*q.v.*). It contains the antitoxic globulins which have a specific power of neutralizing the toxin formed by *Bacillus tetani.*

The tetanus toxin links itself closely to the proteins of the cells of the central nervous system, and when it passes from a wound to the central nervous system it travels along the protoplasm of the nerves. Unfortunately this linking takes place almost coincidently with the appearance of symptoms, and when once the linking has occurred no amount of antitoxin can dislocate it. Hence antitoxin, to be any use, must be given directly the earliest symptoms show themselves. It has been injected directly into the brain in the hope that it may meet and neutralize the toxin before that reaches the nerve cells, or perhaps unite with the cells and thus prevent the toxin from doing so. It is also given subcutaneously, intravenously, directly into the nerve from the wound, and intrathecally. Large quantities of serum thus administered frequently give rise to a plastic, aseptic meningitis. It is very doubtful whether intrathecal serum is of the slightest value. No very striking success has attended its use in man, because, as just pointed out, the tetanus toxin is soon very firmly united with the proteids of the central nervous system. It is stated that success is more likely to be obtained if the patient be chloroformed prior to the intravenous injection. This is explained as being due to chloroform displacing the toxin from combination with the nervous tissues and thus liberating it into the blood stream where it will be neutralized.

The intravenous dose should be 200,000 units. A single administration of this amount will result in a high concentration of antitoxin remaining in the blood for a fortnight, *i.e.* 50,000 units at the end of a week and 20,000 units at the end of two weeks.

There is, however, a certainty that it may benefit if it is given directly after a patient has a wound which is likely to contain tetanus bacilli, *i.e.* such a wound as is contaminated with soil. In the last war English soldiers received as a preventive 500 units subcutaneously as soon as possible after the infliction of a wound, followed by three similar doses at intervals of a week, and there is every ground for believing that this practice was the reason why the deaths from tetanus were few as compared with those in other wars.

TETANUS PROPHYLACTIC

Toxinum Tetanicum Detoxicatum (B.P.). *Synonym.* Tetanus Toxoid. The sterile filtrate of a culture of *Clostridium tetani*, the specific toxicity of which is removed by chemical substances. Formaldehyde was first used for this purpose, and is still for the official preparation unless Alum Precipitated Tetanus Toxoid is prescribed. The latter is the preparation of choice, for it is less likely to cause unpleasant reactions and it gives greater immunity.

Dose, 8—15 min. 0·5—1 ml.—by subcutaneous or intramuscular injection.

It is now clear that a high degree of immunity to tetanus can be obtained by the prophylactic use of tetanus toxoid. The best results are secured by giving two 1-mil doses deeply subcutaneously with an interval of six weeks between them, and a third dose of ½ mil six months later. This final dose is not absolutely necessary but it usually has a remarkable effect in producing a rise of antitoxin titre far in excess of that caused by the first two injections. The incidence of tetanus in British troops in the Middle East (1940–43) who were protected by toxoid was 0·013 per cent., whereas in the South African force, not so protected, it was 0·16 per cent. (Mellanby).

A protected individual should, nevertheless, if the subject of extensive and dirty wounds, be given a prophylactic dose of anti-tetanus serum.

Scarlet Fever Antitoxic Serum. This is prepared, as are other sera, by inoculating a horse with doses of the hæmolytic streptococcus of scarlet fever. It is of great value in severe cases. During epidemics it is of use as a prophylactic. Given intravenously (10 c.c.) in cases of streptococcal septicæmia and also intrathecally if meningitis is present its effect may be dramatic and life-saving.

Dose, Prophylactic, 5—10 ml. (3000—6000 Units); **Therapeutic, 20—50 ml. (12,000—30,000 Units)**; by injection.

Schultz-Charlton Test. This consists of the injection of 0·2 c.c. of a 10 per cent. solution of scarlatinal antitoxin intradermally in an area affected by the scarlet fever rash. In about five hours an area is blanched over 3 to 4 cms. and this persists for one to two days. The test is used for diagnostic purposes. It is also useful if carried out with the patient's serum taken ten days after a suspected attack. If it blanches a scarlet fever rash the donor's disease is established; if not, it is presumed that he did not suffer from scarlet fever.

Dick Test. Similar to the Schick test, but using the filtrate from a culture of *Streptococcus scarlatinæ*. A flush comes on in about five hours and lasts for one to two days in susceptible persons.

Scarlet Fever Prophylactic. This is a sterile filtrate from a culture of *Streptococcus scarlatinæ*, issued in two strengths: (1) containing 2500 skin test doses per c.c., and (2) containing 20,000 doses per c.c.

It is used to protect "Dick-sensitive" individuals in the presence of an epidemic.

Dose, strength (1) at weekly intervals; 500 (0·2 c.c.), 1000 (0·4 c.c.); strength (2) 5000 (0·25 c.c.), 10,000 (0·5 c.c.).

Toxinum Staphylococcicum Detoxicatum (B.P.). Staphylococcus Toxoid.

Dose, ¾ min. gradually increased to **15 min.** } by intramuscular

0·05 ml. ,, ,, ,, **1 ml.** } injection.

Serum Antivenosum (B.P.C.). *Synonyms.* Antivenene, Snake venom Antitoxin. It is made from the horse in the same way as diphtheria antitoxin. It is antitoxic to cobra poison, and is in practice efficacious; probably it is useless for bites by other snakes, but as this is uncertain it should always be given. The serum that is much wanted is a polyvalent one, efficacious for bites by all species of poisonous snakes. Antivenomous serum is given hypodermically.

Dose, at least 100 ml. by intravenous injection.

Antimeasles Serum (Immune). Six c.c. of convalescent serum obtained within three weeks of the fall of temperature to normal will, if injected intramuscularly, produce complete but temporary immunity in about 70 per cent. of cases. The remainder who develop measles have it very slightly.

Antiplague Serum (Haffkine). This is prepared by inoculating buffaloes, sheep and horses with plague bacilli. Usually 50 c.c. are given intravenously, followed by two doses of 50 c.c. subcutaneously in twenty-four hours and smaller doses during the next few days.

GAS-GANGRENE ANTITOXINS

Antitoxinum Œdematiens (B.P.). This serum contains the antitoxic globulins which have the specific power of neutralizing the toxin formed by Clostridium œdematiens. *Strength:* 1500 units per ml.; 15,000 per G.

Dose, by injection: 10,000 Units as prophylactic; not less than 30,000 Units therapeutically.

Antitoxinum Septicum (B.P.). A gas-gangrene serum with a specific power of neutralizing the toxin formed by the Clostridium known as Vibrion Septique.

Dose, by injection: 5000 Units as prophylactic; not less than 15,000 Units therapeutically.

Antitoxinum Welchicum (B.P.). The preparation is similar to that of the other sera. It contains antitoxic globulins which have the specific power of neutralizing the toxin formed by Bacillus perfringens (*Bacillus Welchii*). Standardized by biological assay.

Dose, by injection : 10,000 Units as prophylactic ; 30,000 Units therapeutically.

Antitoxinum Œdematiens Compositum (B.P.). Prepared by mixing antitoxin of œdematiens, perfringens, and septicum.

Dose, 10,000, 10,000 and 5000 Units respectively prophylactic.
30,000, 30,000 and 15,000 Units respectively therapeutically.

The sera are used to prevent and treat gas gangrene occurring in wounds. They are also of value in the prevention and treatment of peritonitis and atony following operations.

Serum Antibotulinum (B.P.C.). *Synonym.* Botulinus Antitoxin. The serum of horses immunized by injections of *Clostridium botulinum.* It must be given early to be of any use, because the toxin has great affinity for nervous tissue and cannot be dislodged.

Dose, Prophylactic, 10 ml. intramuscularly; **Therapeutic, 50 ml.** intravenously.

Antianthrax Serum. This is prepared in the same way as other sera, and its having been used with good results in animals has led to its successful employment for patients suffering from anthrax. The dose is 60 to 80 c.c. intravenously.

GROUP XXXI

Vaccines

Antibody formation is stimulated by injecting subcutaneously into the patient dead bacteria of the variety causing his disease. A preparation of bacteria used for such a purpose is called a vaccine, and the dose is expressed as the number of bacteria injected—*e.g.* we speak of a dose of 5,000,000 of streptococcal or gonococcal vaccine. In the case of tuberculin the vaccine consists of an extract of the dead bacilli.

Sensitized vaccines are sometimes used. They are vaccines in which an emulsion of the micro-organisms is left in contact for several hours with the serum of an animal immunized against the same micro-organism. The micro-organisms attract to themselves the specific antibody in the serum, they gradually sink to the bottom of the vessel, the serum is pipetted off, and we have left a vaccine to which is attached a specific antibody. It is called a sensitized vaccine. Like other vaccines, it is killed before use by heat or the addition of a little carbolic acid. Some authorities consider sensitized vaccines more useful than ordinary vaccines.

Detoxicated vaccines are those in which the endotoxin has been removed from the micro-organisms. The endotoxin passes into a solution, the organisms are precipitated and are used as any other vaccine.

Autogenous vaccines are those prepared from the actual patient for whom they are used.

Stock vaccines are those prepared from any suitable case and kept ready for use when required.

Defatted vaccines. It has been suggested that the therapeutical failure of certain vaccines may be due to the protection of their protein by lipoidal substances, so acetone and formalin have been used to remove the lipoids. Vaccines thus treated are commonly called defatted, which is not strictly accurate, and Dryer proposes instead the word diaplyte, signifying washed through and through.

If the patient is severely and recently ill with a high temperature he is usually so considerably poisoned by the bacteria or their toxins which are causing his disease that the administration of a vaccine will only make matters worse, hence they should not be used at all, or at least in very small doses ; but if the disease is chronic some good may be done by giving a vaccine which presumably acts by raising the various means of resistance to the micro-organism causing his disease. The general condition of the patient—his temperature, pulse, and gain in weight—are indications as to whether vaccine treatment should be continued. Owing to the harm that may follow from a severe negative phase several days' interval (usually seven or ten) must always elapse between the administration of each dose of vaccine, unless very small increments are used.

VACCINE LYMPH

Vaccinum Vacciniæ (B.P.). A preparation of the substance which is obtained from the vesicles produced by the inoculation of vaccinia virus on the skin of healthy animals (usually calves). The lymph is tested to ensure the absence of living gas-producing anaerobes and of hæmolytic streptococci. It is treated with glycerin to reduce the total number of living bacteria to not more than 5000 per mil.

This is the only vaccine which contains living organisms which, when introduced into the skin, produce a mild attack of vaccinia. A person so inoculated has a high resistance towards small-pox, which diminishes over a period of years. Re-vaccination should be carried out every seven years, and more often if exposure to infection is probable. In previously unvaccinated adults, vaccine lymph may, when inoculated, produce a fatal encephalitis. This does not occur in the young and seldom in those already vaccinated. It arises most often when three or more scarifications are made.

Dose, 1 min.—0·06 ml.—by scarification.

OLD TUBERCULIN

Tuberculinum Pristinum (B.P.). The concentrated filtrate from a fluid medium on which the Bacillus Tuberculosis has been grown.

Characters. A transparent, viscous fluid, with an odour like honey.

Dose, $\frac{1}{6000}$—$\frac{1}{60}$ min. 0·00001—0·001 ml. (diagnostic)—by intradermal injection.

N.B. Old Tuberculin prescribed with the suffix T must be prepared from human bacilli ; the suffix PT indicates the bovine type.

Tuberculini Derivativum Proteinicum Purificutum. *Synonym.* Tuberculin P.P.D.

Dose, 0·1 ml. of solutions containing in each ml. P.P.D. equivalent in potency to 0·0001, 0·001, or 0·01 ml. of the standard preparation of old tuberculin. It is used diagnostically intradermally.

Tuberculins. Koch found that by growing tubercle bacilli under certain conditions, the fluid in which they grew contained their toxins. He called the fluid remaining after the bacilli were filtered off, tuberculin, now usually called old tuberculin, the abbreviation for which is T. It is virtually a solution of the toxins in the glycerin in which the bacilli grew. It is a thick, dark yellow fluid.

No effect follows if this is injected into a healthy person, but if he has tuberculosis, the injection produces a high temperature, rigors, a feeling of illness, pains in the joints, sometimes albuminuria and rashes on the skin, and at the same time the lesion is stimulated into activity. These dangerous reactions demand the greatest care in dosage ; the only disease for which its employment might be justified is lupus of the skin, for there the local reaction in the lesions can be watched, and lupus is so chronic that sometimes the stimulation may be useful ; but tuberculin is rarely employed even for lupus.

In most adults some degree of reaction is exhibited to tuberculin tests indicating sensitivity acquired as the result of tuberculosis which has healed.

Koch also prepared an aqueous extract of dried highly virulent tubercle bacilli. He called the upper layers of this extract, Tuberculin O., or shortly T.O. (Oberer Tuberculin). It is rarely used, and its action is the same as that of old tuberculin. The lower layer is dried and re-extracted several times ; the final extract is called new tuberculin, T.R. (T. Rückstand). It produces no visible effects upon healthy people, but when injected in any but minute doses into those suffering from tubercle it leads to the same general reaction as old tuberculin, but usually produces no local reaction upon the tubercular lesion. New tuberculin is rarely used for diagnosis. It is the tuberculin most used therapeutically in man, but a bacillary emulsion (B. E.) is sometimes given. Many think tuberculin often does harm, and unless used with judgment it may produce undesirable general reaction, and speaking generally tuberculin is not now thought to have the high therapeutic value formerly attributed to it.

It occasionally appears to aid the cure of local tuberculosis, especially that of the bladder, skin, and lymphatic glands. If too large doses are given, or if a subsequent dose is given during a negative phase, we see the same evil effects that were observed when tuberculin was first employed by Koch.

B.C.G. Vaccine. This is prepared from the descendants of a tubercle bacillus of bovine origin found in 1908 by Calmette and Guérin to have lost its virulence after successive transfers on a bile-potato medium. It has remained incapable of producing progressive disease even in the guinea-pig.

Administered by scarification or multiple skin puncture it induces tuberculin sensitiveness in previous Mantoux-negatives, and increases resistance to subsequent infection with pathogenic tubercle bacilli. In a large series of cases it reduced the morbidity from tuberculosis from 17·6 to 2·6 per cent. It should not be injected because of the danger of abscess formation.

Mantoux Test. Intradermal. 0·1 mil of a 1 in 10,000 dilution of Tuberculin T. is injected intradermally. In twenty-four to forty-eight hours a red slightly raised erythematous patch 1 to 2 cms. in diameter indicates a positive reaction. In children this is very suggestive of active tuberculosis. In the adult its significance is less, but is strengthened by a positive reaction produced by higher dilutions.

Von Pirquet Test. Scarification. A drop of undiluted Tuberculin T. is placed on the skin, which is scarified through it. A papule of ½ to 1 inch in diameter indicates a positive reaction.

Subcutaneous Test. 0·001 mil is injected subcutaneously. A rise of temperature of 1 to 2° F., with local swelling and increased signs of activity of the suspected lesion, are diagnostic. The test must be used with great care.

Vaccinum Febris Flavæ (B.P.). Yellow fever vaccine. Aqueous suspension of chick embryo infected with strain 17D of Yellow Fever virus. This is not virulent to man.

Characters. Creamy or reddish-yellow, solid, soluble in water.

Dose, not less than 500 LD50—doses by subcutaneous injection.

Vaccinum Typhi Exanthematici (B.P.). Typhus Vaccine. A sterile suspension of typhus rickettsiæ which have been killed.

Dose, 4—15 min. 0·25—1 ml.—by subcutaneous injection.

Vaccinum Pestis (B.P.). Plague Vaccine. A suspension of dead plague bacilli 2000 million per ml.

Dose, 0·5—1 ml.

Cholera Vaccine. Injection of 1000 million dead vibrios and twice this amount a week later gives protection for 3 to 6 months. Serum treatment has been tried, but is useless.

ANTI-TYPHOID-PARATYPHOID VACCINE

Vaccinum Typho-Paratyphosum (B.P.). *Synonym.* T.A.B. Vaccine. A sterile suspension of the micro-organisms B. typhosus, B. paratyphosus A, and B. paratyphosus B, which have been killed. One ml. contains 1000 million B. typhosus, 500 million B. paratyphosus A., and 500 million B. paratyphosus B.

Doses, First dose, 0·25—0·5 ml.
Second dose, 0·5—1 ml. after 7 to 21 days—by subcutaneous injection.

The typhoid and paratyphoid bacilli possess two antigenic substances known as the O and Vi antigens. The latter is the more effective prophylactic agent, but it is labile and largely destroyed if the organisms are destroyed by heat and preserved with phenol. An alcohol-preserved and alcohol-killed vaccine contains a large amount of effective Vi. This form is, therefore, to be preferred. This view has been borne out by experience in the Libyan campaigns of 1940–43. British troops protected with T.A.B. vaccine made from strains rich in Vi antigen suffered to an almost negligible extent from typhoid fever. There was, however, a high endemic rate of the enteric fevers amongst the Germans and Italians who relied on the less potent Vi-poor vaccine.

Local inflammatory reaction with some pyrexia follows the injection in a few hours, but usually soon passes off. Therefore it is best to give the injection in the evening and keep the patient in bed the next day. A second vaccination is performed ten days after the first. The blood serum, in high dilution, of an inoculated person clumps typhoid bacilli for at least six months after an inoculation and in lower dilutions for several years. Injections of vaccine should not be practised upon those in the midst of an outbreak of typhoid fever, because for a short time after inoculation the susceptibility to typhoid is enhanced. This negative phase lasts for about a week and is then followed by the appearance of agglutinins.

The protection afforded by the typhoid vaccine is usually complete for a year and to a less extent for several years subsequently. A massive infection with typhoid bacilli may overcome the protection of recent inoculation, in which case the disease will be attenuated.

It is now customary to protect against typhoid, paratyphoid and tetanus (using the toxoid) by injecting a suitable mixed preparation of antigens. The second dose may follow four weeks after the first to obtain benefit from the tetanus toxoid (*q.v.*) without loss of protective reaction to the T.A.B.

Intravenous injections of 0·1 mil may be given therapeutically to produce rigors and pyrexia in the treatment of gonorrhœal rheumatism.

Hydrophobia Vaccine. A rabbit is inoculated from the spinal cord of an animal dead of hydrophobia, other rabbits are inoculated from the spinal cord of this, and so through a series until the spinal cord (which is the chief seat of the virus in hydrophobia) contains a virus the incubation period of which is seven days. The spinal cord loses its virulence when exposed to the air, so that a series of spinal cords (each of which originally contained a virus the incubation period of which was seven days) can be prepared of greater or less virulence according to the time during which they have been exposed to the air. It is found that if a patient who has been bitten by a rabid dog is inoculated first with a rabbit's spinal cord of a low degree of virulence, and next day with one of a higher degree, and so on increasing the virulence of the injection, hydrophobia does not usually develop in him if the treatment is begun soon after the bite. If the person bitten go for treatment immediately after the bite it is almost certain he will not suffer from hydrophobia. The incubation period of hydrophobia is fortunately several weeks, and hence if the above treatment is carried out it renders the patient immune before the incubation period expires.

The **B.P.** also contains :—

Vaccinum Acnes.
— Choleraicum.
— Dysentericum (Flexner).
— Pertussis.
— Staphylococcicum.
— Tuberculinum.

GROUP XXXII

Vitamins

Vitamins are substances occurring in various foods, which are essential for the maintenance of good health. In the absence of one or more of them, a diet, otherwise perfectly balanced, will fail to maintain health ; in fact, a deficiency disease, of type according to the missing vitamin, will arise. The administration of the necessary vitamin results in rapid cure of the illness. The majority of the vitamins have now been isolated and their chemical structure has been determined. Some can be synthesized. The amount necessary to maintain health is extremely small and clearly bears no relationship to energy value. They are easily oxidized and are liable to destruction by food preservatives.

Assay. The potency of vitamin preparations is assayed by testing their efficacy in producing recovery from the corresponding vitamin deficiency disease. The League of Nations standard has been adopted internationally for comparison, and strength is expressed in terms of units.

Biosynthesis. It was shown first in rats that vitamin B_1 could be produced in the gut as the result of microbial activity on a starch diet. This was known as *refection.* It is now known that human intestinal flora can produce all the components of vitamin B in this way and also vitamin K. If a patient on a low intake of vitamin B be given succinyl sulphathiazole, signs of vitamin deficiency may arise owing to sterilization of the gut.

Vitamin A

Liquor Vitamini A Concentratus (B.P.). Contains 50,000 Units of vitamin A in 1 G.

Dose, 1—10 min. 0·06—0·6 ml. (2500—25,000 Units)—daily.

Vitamin A is a colourless crystalline, thermostable, hydrocarbon $(C_{20}H_{28})H.OH$, first isolated in 1937. It is fat-soluble. It occurs only in animal products, *e.g.* milk, butter, halibut-liver oil, and cod-liver oil. It is absorbed completely and is stored in the liver. The body can, however, obtain this vitamin from green vegetables and carrots which contain carotene $(C_{20}H_{28})_2$, a yellow pigment which is converted to true vitamin A by the liver. Carotene is not present in fish-liver oil. Only about one-third of carotene in food is absorbed and converted into vitamin A.

Deficiency. The function and structure of the epithelial cells of the body depend upon an adequate supply of vitamin A. If this fails, epithelial atrophy occurs with secondary proliferation of the basal cells. The growth of these replaces the atrophied epithelium with stratified, keratinizing epithelium. The absence of vitamin A from the diet affects the growth of immature animals, in that they fail to gain weight rather than length. Xerophthalmia, ulceration of stomach and duodenum, and a general lowering of resistance, especially of the mucous membranes, with tendency to the development of respiratory catarrhs, and faulty dentition also arise.

In humans hyperkeratosis of the pilo-sebaceous follicles on the anterior and lateral aspects of the thighs and back and sides of forearms (phrynoderma) occurs as the result of vitamin A and of vitamin C deficiency.

Vitamin A deficiency is responsible for **xerophthalmia** and keratomalacia that cause most of the preventible blindness in children in India. This disease was prevalent in Denmark in 1917–1918 because that country exported so much of its fresh products to Germany. The formation of **renal calculi** is also favoured owing to the shedding of epithelial *débris*. Other diseases from the same cause are "**toad-skin**" in Ceylon, **faulty development of teeth,** unhealthy gums and **night-blindness.** The last is due to disappearance of visual purple (rhodopsin) in the rods. It is formed from vitamin A and protein. Exposure of the retina to light breaks down the visual purple and the vitamin is set free. Some of this is destroyed in the process, consequently if food supplies are inadequate regeneration of the visual purple in the rods is imperfect and night vision and dark adaptation are impaired.

Minimum Requirement. An adult should receive at least 3,000 units of vitamin daily. Growing children and pregnant women need twice this amount.

Vitamin B

Aneurinæ Hydrochloridum (B.P.). Aneurine Hydrochloride. *Synonyms.* Vitamin B_1; Thiamine Hydrochloride.

Dose, $\frac{1}{60}$—$\frac{1}{20}$ gr. 1—3 mg.—prophylactic (daily).
$\frac{1}{6}$—$\frac{1}{2}$ gr. 10—30 mg.—therapeutic (daily).

Preparations (**B.P.**)

1. **Injectio Aneurinæ Hydrochloridi.** *Synonym.* Injection of Vitamin B_1. Contains 25 mg. ($\frac{2}{5}$ gr.) in 1 ml. (15 min.).
Dose, $\frac{1}{6}$—$\frac{1}{2}$ gr. 10—30 mg.

2. **Tabellæ Aneurinæ Hydrochloridi.** Contains 1 mg. ($\frac{1}{60}$ gr.).

Vitamin B has been shown to be composed of several different substances; the most important therapeutically are aneurine (thiamine), riboflavin, and nicotinic acid and folic acid. They are water-soluble and associated with the metabolism of glucose. A high carbohydrate diet is prone therefore to reveal latent B-complex deficiency. The dependence of the nervous system on glucose explains its susceptibility to vitamin B lack.

Aneurine (Vitamin B_1) has been isolated as the hydrochloride ($C_{12}H_{16}N_4OS, 2HCl$) and is the only one known to contain sulphur. It does not occur in high concentration in any food, but on the other hand it is present in a great variety of foods. In these ways it differs from the others. It is water-soluble and has been synthesized. It is not fat-soluble, and is destroyed by boiling. It is present in many plants, particularly in seeds, nuts, celery, lettuce, the outer layers of cereals, asparagus, egg-yolk, peas, beans, bran, milk, liver, kidney and heart. It is present in yeast and wholemeal bread, but not in white bread.

Deficiency. Deficiency of the vitamin is caused by diminished intake (unbalanced diet, alcoholism, vomiting), diminished absorption (achlorhydria, carcinoma of stomach, prolonged diarrhœa), or increased demand for vitamin B_1 (pregnancy, lactation, prolonged fever). Its absence from food produces intestinal atony, constipation, *Bacillus coli* infection of the urine, **polyneuritis,** emotional instability, mental depression and other symptoms often attributed to psychoneurosis, and fall of temperature. In well-marked cases of vitamin B deficiency presenting polyneuritis, or cardiac weakness and œdema, the condition is known as **beri-beri.**

Beri-beri was the scourge of the Japanese navy for many years because the men ate rice as their staple article of food. It was the introduction of polished rice free from husk that started the trouble, which was promptly cured by the addition of rice polishings to the food.

Aneurine acts as a catalyst in the normal oxidation of pyruvic acid, an intermediate breakdown product of glucose. Lactic acid accumulates in beri-beri, as also its derivative pyruvic acid, giving rise to the convulsions seen in animal beri-beri and to the bradycardia and neuritis in human beings. These acids interfere with oxygen use by the tissues.

In cases of chronic gastritis, alcoholism, achylia, pyloric obstruction, or prolonged vomiting from any cause, or in chronic diarrhœa, **acute polyneuritis** may arise from lack of vitamin B_1 absorption. An individual whose intake of the vitamin is just sufficient for health may develop polyneuritis if the basal metabolic rate becomes raised, *e.g.* in pregnancy or lactation, for then the supply of vitamin B_1 is inadequate for the increased oxidation demands. The same will occur if the diet contains a high proportion of carbohydrate. The polyneuritis of alcoholism is probably the result of deficient vitamin intake, for the appetite of alcoholics is notoriously bad. It may also be due to deficient absorption arising from achlorhydria secondary to gastritis. Experimentally it has been shown that incubation of vitamin B_1 with achlorhydric gastric juice, or with gastric juice, and blood diminishes the available amount. Deficiency of the vitamin will of itself produce achlorhydria. This type of polyneuritis responds well to the injection of 0·01 grm. of aneurine daily. Benefit should be observed in two to three weeks.

Refection. This term is applied to an interesting phenomenon in connection with vitamin B_1 deficiency in the food of rats. They show no sign of disease if raw starch is present in the diet. The explanation is that microbial activity in the gut acting on the starch produces vitamin B_1.

Minimum Requirement. This varies with the amount of carbohydrate taken. 1 mgm. daily may be accepted as an approximate figure.

Vitamin B_2 was at one time a term used to embrace nicotinic acid, riboflavin, and certain vitamins of no immediate importance to human beings. They are all, together with vitamin B_1, included in the vitamin B complex and share in common their natural occurrence in the same or similar foods and their water-solubility. *It follows that except under experimental conditions it is most improbable that a pure deficiency of any one of the members of the complex will be encountered—a point which should be borne in mind in relation to therapeutics.* The term vitamin B_2 if used at all is now employed in reference to the anti-pellagra vitamin which is probably identical with the amide of nicotinic acid.

Vitamin B_2 was recognized as distinct from B_1 from certain differences, viz. :—

1. The purer the preparation of anti-beri-beri vitamin the less effective it became on pellagra.
2. B_1 is present in maize-meal extract : B_2 is not.
3. B_2 is more thermostable.
4. B_2 is less soluble in alcohol.
5. Liver extract is rich in B_2, but poor in B_1.

Acidum Nicotinicum (B.P.). $C_5H_4N.COOH$.

SOURCE. From nicotine by oxidation.

CHARACTERS. White, feebly acid crystals. *Solubility* : 1 in 75 cold water ; freely in boiling water and in solutions of alkalies.

Dose, ¼—½ gr. **15—30 mg.**—prophylactic.
¾—4 gr. **50—250 mg.**—therapeutic, daily.

Preparation (**B.P.**)

Tabellæ Acidi Nicotinici. Contain ⅘ gr.—0·05 G. in each.

Nicotinamidum (B.P.). $C_5H_4N{\cdot}CONH_2$.

Synonym. Nicotinic Acid Amide.

CHARACTERS. Crystalline, bitter powder. *Solubility* : 1 in 1 of water.

Dose. As for Nicotinic Acid.

Preparation (**B.P.**)

Tabellæ Nicotinamidi. Contain ⅘ gr.—0·05 G. in each.

The usual sources of nicotinic acid are meat and wholemeal bread.

Deficiency. **Pellagra** results from vitamin B_2 lack. It occurs extensively in the Southern States of America where the diet of the poorer classes consists largely of maize-meal, molasses and meat (salt-pork). It is common also in Egypt and Italy. The chief symptoms are stomatitis, often with invasion by Vincent's organisms, glossitis, diarrhœa, dermatitis, and dementia. Fatigue, tachycardia, and depression may be the earliest symptoms. If nicotinic acid be given in **0·25 to 0·5 grm. in divided doses** daily full recovery takes place in two to three weeks. The amide being more soluble is suitable for injection. At first an exacerbation of the dermatitis may be observed.

The administration of nicotinic acid or its amide by mouth or by injection may shortly be followed by dizziness, tingling of the extremities and flushing of the skin. The symptoms are transient.

Minimum Requirement. The adult is liable to develop pellagra on an intake of less than 20 mgm. daily. For health it seems probable that 100 mgm. are required.

Riboflavina (**B.P.**). *Synonyms.* Riboflavin; Lactoflavin. $C_{17}H_{20}O_6N_4$.

SOURCE. From yeast or by synthesis.

CHARACTERS. Orange-yellow, crystalline powder. Slightly soluble in water; more so in saline.

Dose, $\frac{1}{60}$—$\frac{1}{6}$ **gr.** **1—4 mg.**—prophylactic.
$\frac{1}{12}$—$\frac{1}{6}$ **gr.** **5—10 mg.**—therapeutic.

Riboflavin occurs with the other members of the B-complex in the foods mentioned under B_1. Meat and milk are important sources of supply.

Deficiency. **Cheilosis** results from lack of riboflavin. It consists of reddening and soreness of the lips especially along the line of closure, and fissuring at the angles of the mouth. This may be associated with greasy desquamation in the naso-labial folds, and in the ears, eyelids, alæ nasi and nasal vestibule. Lack of energy, palpitation, depression and inability to concentrate often precede the development of cheilosis. It is very common to find a combination of nicotinic acid and riboflavin deficiency.

Angular stomatitis alone should not be regarded as evidence of vitamin deficiency. It may result from any condition encouraging profuse salivation, *e.g.*, post-encephalitic parkinsonism, or the use of chewing gum.

Invasion by capillaries of the cornea around the inner margin of the limbus is another characteristic of riboflavin deficiency.

Minimum Requirement. This varies with the amount of carbohydrate in the diet. Probably 2 mgm. daily are sufficient.

Pyroxidine (Vitamin B_6). Its function is probably associated with the utilization of unsaturated fatty acids.

Dose, 0·1—0·2 G.

It has been used in the muscular dystrophies. Insomnia, irritability, and pains in the limbs may persist in beri-beri if treated only with B_1, but disappear if pyroxidine be given.

It has been claimed that pyroxidine stimulates granulocyte production, and that it may thus overcome the agranulocytosis which may be caused by thiouracil and other drugs. The dose recommended is 150 mgm. daily intravenously for 10 days. An improvement in the blood-count is to be expected by the third day.

Folic Acid. A crystalline substance originally isolated from spinach and other green leaves and grasses. It is a constituent of the vitamin B group. It has been synthesised and shown to be pteroylglutamic acid.

Dose (provisional), **10—30 mg.** by mouth or intramuscular injection.

Therapeutics

Of great value in the treatment of megaloblastic anæmias with megaloblastic change in the bone marrow, *i.e.*, pernicious anæmia, pellagra, sprue, steatorrhœa and pernicious anæmia of pregnancy. It should not be used for pernicious anæmia because it is less effective than liver, and does not prevent the development of subacute combined degeneration. It acts equally well if given by mouth or injection.

Vitamin C

Acidum Ascorbicum (B.P.). $C_6H_8O_6$. *Synonym.* Vitamin C. *Unoff. Synonym.* Cevitamic acid.

Source. Obtained from the ripe fruit of *Capsicum annuum* and other vegetable sources, or by synthesis.

Characters. Colourless crystals ; odourless ; taste of lemon ; water-soluble.

Dose, ⅖—1¼ gr. **25—75 mg.**—prophylactic (daily).
3—8 gr. **0·2—0·5 G.**—therapeutic (daily).

Preparation (B.P.)

Tabellæ Acidi Ascorbici. Contain ⅘ gr.—0·05 G. in each.

Vitamin C has been isolated and synthesized in crystalline form and shown to be identical with hexuronic acid, which has been renamed ascorbic acid. It is water-soluble and occurs naturally in orange, lemon, cabbage, tomato, green vegetables, black currant, rose-hips, and in high quantity in the adrenal cortex; next to this in value comes horse-radish. Limes are not so rich as lemons, and the preserved juice still less so. Most animals are capable of synthesizing vitamin C in the body; man, monkeys, and guinea-pigs cannot do so, however.

It appears that the vitamin is concerned with furthering the oxidation-reduction processes in the body and is thus essential to cellular function and repair.

Vitamin C is excreted in the urine and can be analysed quantitatively, because it reduces the blue dye dichlorophenolindophenol to a colourless derivative.

Deficiency. Absence of this so-called "anti-scorbutic" vitamin was responsible for terrible ravages by **scurvy** in the crews of sailing vessels and amongst explorers in the polar regions. The provision of lemon-juice brought this to an end.

The disease is characterized first by fatigue followed later by spongy, bleeding gums and bleeding in various parts of the body, especially under the skin and into the joints. Wounds will not heal and fractures fail to unite.

Deficiency of vitamin C results in faulty development, and imperfect preservation, of the teeth.

Minimum Requirement. If less than 10 mgm. ascorbic acid be taken daily signs of deficiency are likely to develop. At least 20 mgm. should be taken daily.

Vitamin D

Liquor Vitamini D Concentratus (B.P.). Contains 10,000 Units of vitamin D in 1 G.

Dose, 1½—6 min. 0·1—0·4 ml. (1000—4000 Units)—prophylactic.
3—30 min. 0·2—2 ml. (2000—20,000 Units)—therapeutic daily.

Liquor Vitaminorum A et D Concentratus (B.P.). Contains in 1 grm. 50,000 Units vitamin A and 5000 Units of vitamin D.

Dose, 1—10 min. 0·06—0·6 ml.—equivalent to **vitamin A 2500—25,000 Units; vitamin D 250—2500 Units.**

CALCIFEROL

Calciferol (B.P.). $C_{28}H_{43}OH$.

Source. Ergosterol in solution is subjected to ultra-violet irradiation; the unchanged ergosterol is separated from the residue. From the latter calciferol is obtained.

Characters. Colourless and odourless crystals insoluble in water; soluble in alcohol and vegetable oils.

Dose, $\frac{1}{2400}$—$\frac{1}{600}$ **gr. 0·025—0·1 mg. (1000—4000 Units)**—prophylactic, daily.
$\frac{1}{1200}$—$\frac{1}{120}$ **gr. 0·05—0·5 mg. (2000—20,000 Units)**—therapeutic, daily.

Preparation (B.P.)

Liquor Calciferolis. Contains in 15 min. 3000 Units of antirachitic activity.

Dose, 5—20 min. 0·3—1·2 ml. (1000—4000 Units)—prophylactic, daily.
10—100 min. 0·6—6 ml. (2000—20,000 Units)—therapeutic, daily.

Vitamin D was identified from vitamin A by the fact that hot air blown through cod-liver oil destroys the latter only. Irradiation of pure cholesterol does not produce vitamin D. Ergosterol was found to be the potent impurity. Irradiation produces from this vitamin D which is calciferol.

Vitamin D is fat-soluble. It is present in cod-liver oil, halibut-liver oil, egg-yolk, butter, milk and green vegetables. Exposure to sunlight or to the ultra-violet rays acts on the ergosterol in the skin, which accounts for the beneficial effect of sunlight in cases of rickets. It acts by raising the P × Ca product in the blood by aiding absorption of calcium and phosphorus from the gut, and also by assisting utilization in bone.

Deficiency. The absence of vitamin D from food results in the characteristic changes of **rickets,** *e.g.* faulty bone development, increased loss of calcium and phosphorus, carious teeth, stunted growth and lowered resistance. It is used in its natural form, as irradiated ergosterol, or as calciferol, in the treatment of rickets, and in the prevention of carious teeth in children. For the latter purpose it should be given to the pregnant mother. It is used also in the treatment of osteomalacia with success.

Minimum Requirement. Infants under six months should have not less than 200 units daily; over six months they should have 400 units daily. The adult, especially the pregnant woman, should take 800 units daily.

Hypervitaminosis. Overdosage with vitamin D will produce lethargy, renal calculi, calcification of vessels and ankylosis of teeth to jaw. It should be noted that crystalline calciferol is 400,000 times more active than cod-liver oil. In the condition of hypervitaminosis the blood phosphorus rises to 8 mgm., the calcium to 15 mgm. or more per 100 c.c., the normal figures being 4 and 10. In rickets they are 3 mgm. and 7 mgm. respectively.

COD-LIVER OIL

Oleum Morrhuæ (B.P.). The oil expressed from the fresh liver of the cod, *Gadus morrhua*, by a heat not exceeding 85° C. and from which the solid fat has been separated by filtration at 0·1 C. Norway coast.

Characters. Pale yellow, with a slight fishy odour, and a bland fishy taste. Sp. gr. **0·922 to 0·929.**

Composition. The chief constituents are—vitamins A and D, unsaturated fatty glycerides, a highly unsaturated acid and cholesterol. *Strength.* 1 G. contains 600 Units of vitamin A activity, and 85 Units of vitamin D activity.

Dose, 60—180 min. 4—12 ml.—daily, in divided doses.

Preparations (B.P.)

1. **Extractum Malti cum Oleo Morrhuæ.** Extract of malt with cod-liver oil. Contains 15 per cent. of cod-liver oil.

Dose, 60 min.—1 fl. oz. 4—30 ml.

2. **Emulsio Olei Morrhuæ.** Emulsion of cod-liver oil. Contains 50 per cent. of cod-liver oil.

Dose, 120—360 min. 8—24 ml.—daily, in divided doses.

Action

Internal. *Gastro-intestinal tract.* Cod-liver oil, even more than other oils, is liable to cause indigestion, nausea, and sickness. Large doses may set up diarrhœa. It is **more readily absorbed** than other oils. Some authorities believe that the superior absorbability of cod-liver oil depends upon its containing more unsaturated fatty acids than other oils, and also to its emulsifying more easily.

Metabolism. Cod-liver oil owes its therapeutic value mainly to its content of vitamin D (anti-rachitic) and also vitamin A.

Therapeutics

Internal. Cod-liver oil and the vitaminized oil preparations are of great service in **rickets,** vitamin D rendering it a specific, and its power of aiding the absorption of calcium and phosphorus being of great service. For the same reason they are valuable in the prevention and treatment of **osteomalacia.** On account of high food value it is useful for any chronic disease associated with loss of flesh, such as tuberculosis, convalescence from acute disease, tertiary syphilis and starvation.

Sodii Morrhuas (B.P.C.). Sodium Morrhuate. The sodium salt of the acids of cod-liver oil.

Preparation (B.P.C.)

Injectio Sodii Morrhuatis. A 5 per cent. solution in water containing alcohol and chlorocresol.

Dose, 8—75 min. 0·5—5 ml.—by intravenous injection, as a sclerosing agent.

Therapeutics

The use of sodium morrhuate in the treatment of leprosy and glandular tuberculosis has fallen into disrepute. The drug is employed extensively in the treatment of varicose veins. It is less certain in its action that quinine-urethane solution, but does not cause sloughing if some escapes into the subcutaneous tissues. The clot following its use is less firmly anchored to the vein wall than that caused by quinine, and embolism has occasionally followed its employment. Sensitivity to morrhuate shown by collapse, or by eczema, occurs in 5 per cent. of patients. Severe allergic reactions may arise in asthmatics and other subjects of allergy if injected with sodium morrhuate.

HALIBUT-LIVER OIL

Oleum Hippoglossi (B.P.). The oil expressed from fresh, or suitably preserved, halibut liver. Contains not less than 30,000 Units of vitamin A in each gramme.

Dose, 1—8 min. 0·06—0·5 ml.: equivalent to **vitamin A 1500—12,000 Units**—daily.

Uses

Halibut-liver oil is particularly rich in vitamin A but also contains a variable amount of vitamin D

(2500 to 3500 units per grm). It may thus be used as a supply of either vitamin and is often reinforced with vitamin D when used in the prophylactic treatment of rickets. The small bulk of an effective dose renders it very suitable for children.

Vitamin E

This fat-soluble thermostable vitamin has been isolated. It is an alcohol probably of the formula $C_{29}H_{50}O_2$. It occurs naturally in wheat-germ oil, seeds, green leaves, oats, and corn.

Deficiency. Its absence from diet results in **sterility** in both sexes. In the male this is caused by degeneration of the seminiferous epithelium. In the female the embryo dies in the second week of gestation. Sexual power is unaffected. There is no evidence that vitamin E deficiency occurs in humans. It is claimed that muscular dystrophies respond to vitamin E medication.

Vitamin K

This occurs in alfalfa, sprouting oats, spinach and many vegetable oils. It has been isolated and proved to consist of two substances (K_1 and K_2), both derivatives of naphthoquinone.

Menaphthonum (B.P.). *Synonym.* Menadione.

CHARACTERS. Yellow, crystalline powder which decomposes on exposure to sunlight. Soluble in fixed oils.

Dose, $\frac{1}{60}$—$\frac{1}{12}$ gr. 1—5 mg.—by intramuscular injection.

Preparation **(B.P.)**

Injectio Menaphthoni. Contains 5 mg. ($\frac{1}{12}$ gr.) in 1 ml. (15 min.).

Dose, $\frac{1}{60}$—$\frac{1}{12}$ gr. 1—5 mg.—by intramuscular route.

Acetomenaphthonum (B.P.).

CHARACTERS. White, crystalline powder. Soluble in boiling alcohol and in acetic acid.

Dose, $\frac{1}{30}$—$\frac{1}{6}$ gr. 2—10 mg.

Preparation **(B.P.)**

Tabellæ Acetomenaphthoni. Contains 5 mg.

Menaphthone has the action of vitamin K. It is given as a 0·5 per cent. oily solution by intramuscular injection. It must not be given by mouth because it irritates the gastric mucosa.

Acetomenaphthonum has the same action but is less irritant and can be given by mouth. It is used chiefly to prevent **neonatal hæmorrhage** and may be given to the mother for a week before labour is expected.

Deficiency. Avitaminosis K is rare because of the capacity of intestinal flora to synthesize it when deficiency in the diet exists. A vitamin K lack normally develops in new-born children but disappears in a week. When this is exaggerated severe hæmorrhages and jaundice develop. The characteristic of deficiency of vitamin K is a tendency to bleed due to **inadequate formation of prothrombin**: the clotting time is thus prolonged. Vitamin K is necessary for the formation of prothrombin by the liver. It is not absorbed from the intestine in cases of **obstructive jaundice** because it needs bile salts for this process. It is either not absorbed or inadequately absorbed in ulcerative colitis, sprue, intestinal obstruction and polyposis. The hæmorrhagic tendency can be overcome by the oral administration of 0·2 grm. daily together with 2 grm. bile salts or by injection of a vitamin K analogue. **Icterus gravis neonatorum** also responds to such injections, which are given intramuscularly. Bleeding is controlled in 2 hours.

Vitamin K is useless to control bleeding produced by dicoumarol (*q.v.*). It is valueless in the hypoprothrombinæmia of severe liver disease. It will prevent the hypoprothrombinæmia induced by large doses of salicylates. One mgm. will counteract 1 grm. of aspirin in this respect.

Vitamin P

Vitamin P has not been isolated. It exists in fruit, vegetables, and cotton-seed oil. It is relatively thermostable.

Deficiency. Lack of vitamin P results in increased capillary fragility and thus **purpura.**

GROUP XXXIII

NUCLEIC ACID AND NUCLEOTIDES

Nucleic acid and its derivatives have long been known to have a stimulating action on the bone marrow with the production of a polymorphonuclear leucocytosis of moderate degree. For this purpose 2 to 10 c.c. of 2 per cent. **Sodium nucleinate** may be given intramuscularly. Pentose nucleotides have been claimed to be far more active in causing leucocytosis. They are marketed as **Pentnucleotide** (nucleotide K—96). Ten c.c. are injected intramuscularly daily in cases of agranulocytic angina and other neutropœnic states. A rise in white cells may be observed in 3 to 5 days, and injections must be continued for a further period of 3 to 6 days if improvement is to be maintained. Several cases of the hitherto fatal agranulocytic angina have recovered apparently as the result of this treatment.

Alarming symptoms of substernal tension, faintness and sensation of dying may follow immediately upon the injection. It is advisable to test the susceptibility of the patient with a preliminary dose of 5 c.c.

Apart from the greater response called forth by pentnucleotide, it possesses the further advantage over sodium nucleinate of not producing an initial negative phase (leucopenia).

GROUP XXXIV

Anticoagulants

Heparin, Dicoumarol

Certain anticoagulants are of use only in the prevention of clotting of blood outside the body. Thus sodium or potassium citrate, oxalate or fluoride fall into this group. Their use is mainly to preserve blood from clotting prior to some chemical estimation which has to be carried out.

Injectio Sodii Citratis Anticoagulans (B.P.). Contains 2·5 per cent. sodium citrate and 0·9 per cent. sodium chloride in sterilized water.

Injectio Sodii Citratis cum Dextroso (B.P.). Details for preparation for use in transfusion are given in a monograph.

Sodium citrate is extensively used in a concentration of 0·25 per cent. in the preparation of blood for transfusion. The potassium salt would be unsuitable for this purpose because of the toxic action of the potassium ion.

Powdered potassium oxalate is often used as an *in vitro* anticoagulant. The blood cells are well preserved and blood can thus be collected and transported to more convenient surroundings for cytological examination. Fluoride must not be used for this purpose because the blood cells are disintegrated by it. It is, however, eminently suitable for the preservation of blood to be examined for urea, uric acid, or sugar content, in fact for the last it is the only satisfactory anticoagulant in that it prevents glycolysis which otherwise takes place in stored blood.

Both oxalate and fluoride are too poisonous for use in blood transfusion.

The above substances act by the removal of ionized calcium. They cannot be used to prevent clotting *in vivo* because, quite apart from the specific toxicity of oxalates and fluorides, to be effective they would have to reduce the calcium to a level incompatible with life.

The citrates have no effect on clotting when given by mouth for they are oxidized to carbonates in the tissues.

Anticoagulants in vivo

The Trypanocide Suramin (Bayer 205, Germanin) is such an anticoagulant acting by raising the resistance of fibrinogen to coagulation. Various dyes have the same effect.

Other substances, notably hirudin from the leech, act by neutralizing thrombin and are known as antithrombic anticoagulants. The greatest advance in the direction of the use of anticoagulants on the living body was made in the discovery of heparin and dicoumarol.

HEPARIN

Heparinum (B.P.). SOURCE. Derived originally from dog liver ; recently from the liver, lung and skeletal tissue of the ox. It arises in the mast cells of the tissues. The liver capsule and lungs are rich in it.

CHARACTERS. Methods of purification have produced a crystalline barium salt of uniform potency. If this be treated with ammonium carbonate solution the barium is removed.

Heparin is then precipitated with acetic acid, washed with ether, and dried. It is then in the form of a powder suitable for storage. For use, a 5 per cent. solution containing 0·25 per cent. of tricresol is prepared.

COMPOSITION. A nitrogenous carbohydrate derivative (mucoitin) combined with sulphuric acid as an ester (up to 35 per cent. SO_4). It contains not less than 75 Units per mg.

Benzidine-heparin ($C_{25}H_{65}O_{50}N_2S_5$) is a compound which is absorbed slowly and thus possesses similar advantages over heparin as does zinc-protamine-insulin over insulin.

Dose, 6000—12,000 Units.

Preparation (B.P.)

Injectio Heparini.
Dose, as above.

Action

Heparin delays the clotting of blood if introduced into the body or if added to the blood after its withdrawal. Its mode of action is not fully understood. It possibly retards the conversion of prothrombin to thrombin and certainly has a direct antithrombic activity. Thrombokinase can overcome the action of heparin not by direct neutralization but by accelerating the prothrombin → thrombin action so that the amount of the latter exceeds the antithrombic activity of heparin. It inhibits platelet agglutination and thus the formation of thrombokinase.

If heparin be added to blood after its withdrawal in a dose of 5 mgm. per 100 mils the coagulation time is extended from the normal four to five minutes to a minimum of forty-five minutes; an average of 100 minutes; and a maximum of sixty hours. If the interior of the blood-containing vessel is paraffined the clotting may be delayed three to five times longer.

When heparin is injected intravenously in a dose of $\frac{1}{2}$ mgm. per kilo. and some blood withdrawn ten minutes later, the clotting time is raised from fifteen minutes to forty-five minutes, 1 mgm. per kilo. raising it to one to one and a half hours. The effect is most marked during the first half-hour after administration; it passes off completely in one and a half to two hours. The bleeding time is unaffected.

Purified heparin is absorbed after subcutaneous injection and acts in a similar way.

Heparin appears to be relatively non-toxic, as much as 4 mgm. per kilo. having been given without untoward effect, except for a transient urticaria.

A certain threshold value must be reached before the anticoagulant action is observed. This is 0·25 mgm. per kilo. of body weight. It is this fact which explains the immunity of a recipient of heparinized blood from further bleeding due to the drug, for on entering the body it is diluted to below the threshold value.

Benzidine-heparin, owing to its slow absorption after subcutaneous injection, causes a prolonged moderate increase of coagulation time, *e.g.* C.T. fifteen minutes for six hours.

Therapeutics

Heparin may be used for **blood transfusion.** The substance is injected into a vein of the donor and blood is withdrawn ten minutes later. For reasons stated it can then be introduced into the blood stream of the recipient without fear of encouraging further bleeding. The method simplifies transfusion technique, and obviates the possibility of unpleasant reactions from the use of sodium citrate. Should the donor receive a severe injury within two hours of heparin administration, his condition would be doubly dangerous on account of hæmorrhage from large vessels. Minor injuries would be unaffected as the bleeding time is not prolonged by heparin.

It is employed to prevent **thrombosis** after operations by continuous administration after a post-operative interval of twelve to twenty-four hours, or it may be so administered in combination with dicoumarin by mouth (*q.v.*). Animal experiments starting with 40 units per kilo. intravenously as an initial dose and followed by 30 units per kilo. per hour will maintain the clotting time at twenty to thirty minutes. In man the subcutaneous administration of benzidine-heparin would probably be more satisfactory. Heparin has been given intravenously at the rate of 20 mgm. per hour. This keeps the coagulation time at about three times the normal. As operations on the female pelvic organs provide the greatest proportion of thromboses and embolism the method might well be tried out here.

Several cases of **bacterial endocarditis** have been treated with intravenous heparin and sulphapyridine by mouth. A priming injection of 1 mgm. per kilo being followed by drip administration of 15 mgm. per hour in normal saline. Not more than 1½ litres should be given daily. The aim is a fourteen-day course. Results have been uniformly disappointing, death usually arising from cerebral hæmorrhage or embolism.

It seems probable that in adequate dosage the condition of **thrombo-phlebitis migrans** might be arrested. Dicoumarin is more suitable. The administration of heparin after the occurrence of coronary or of retinal thrombosis can aim only at prevention of an extension of the clot or of the formation of an intracardiac thrombus.

Heparin may be used as an anticoagulant when collecting blood for various laboratory tests (except the Wassermann) provided that the examination will be carried out promptly.

The anticoagulant effect of heparin is antagonized by trypsin, thrombokinase, snake venom, and blood transfusion.

DICOUMAROL

Dicoumarol (B.P.). *Synonym.* Dicoumarin. 3·3′-methylene-bis-(4-hydroxycoumarin).

SOURCE. A substance occurring in improperly cured sweet-clover silage. It arises from conversion of coumarin which is the aromatic bitter tasting substance in sweet clover. It is now prepared synthetically.

CHARACTERS. A white crystalline substance, slightly soluble in water; readily in alkaline solutions.

HISTORICAL. A hæmorrhagic disease of cattle often ending fatally had long been familiar to breeders and veterinary surgeons. Schofield, of Canada, in 1921 traced the source of this to the eating of spoiled sweet-clover. Link, of America, as the result of seven years of research reported in 1941 on the isolation and synthesis of the hæmorrhagic agent. Clinical trials were started in the same year.

Dose, ¾—5 gr. 50—300 mg.

Action

Spoiled sweet-clover, and thus dicoumarin, produces hæmorrhage by delaying the coagulation of the blood by reduction of the prothrombin content. Under dicoumarin clotting does not occur in cannulæ introduced experimentally into the arterial lumen.

Prothrombin, a protein, occurs in blood plasma in a concentration of 40 mgm. per cent. It is converted into thrombin by thrombokinase in the presence of ionized calcium. The liver is its chief source and vitamin K is important to its formation. A reduction of prothrombin concentration to less than 35 per cent. of normal produces a hæmorrhagic state.

Thrombokinase (thromboplastin), a lipoprotein, occurs in all tissues, especially the platelets. It affects the velocity of prothrombin to thrombin conversion and not the quantity.

Thrombin converts 2,000 times its weight of fibrinogen to fibrin. Fibrinogen is produced in the liver.

The prolongation of prothrombin time by dicoumarin indicates either destruction of prothrombin, or suppression of its action, or inhibition of its formation. The first is improbable because dicoumarin has no influence on the clotting of drawn blood. In all probability it acts by reducing the formation of prothrombin. It has been shown that the drug will undergo degradation to salicylic acid. It is probable that its effect is due to a breakdown product of this acid in the liver (*cf. salicylates: metabolism*; p. 311) a fact which will explain the lag in dicoumarol action. It has no effect on capillary fragility, bleeding time, hepatic function, blood cells, blood urea, or icteric index. It raises the erythrocyte sedimentation rate and retards clot retraction. After death produced by overdosage the only autopsy changes are those referable to widespread hæmorrhages. Dogs kept on non-fatal doses of dicoumarin sufficient to prolong the prothrombin time have, over a period of six to seven years, died no sooner than controls. There is thus strong evidence of the non-toxic nature of the drug apart from its specific action.

The normal prothrombin time is ten to fifteen seconds. Between the time of administration of dicoumarin and the development of prolongation of the prothrombin-time there is a considerable interval, *i.e.* from twenty-four to seventy-two hours. This lag is the same whether the drug be given by mouth or injected intravenously as the disodium salt. The effect of dicoumarin on the coagulability of the blood takes two to ten days to pass off.

Dosage

The quantity of dicoumarin to be administered is controlled by the variations in the prothrombin time. Experience suggests that to be of therapeutic benefit this time should be raised 50 per cent. Although the coagulation time is prolonged its estimation is not sufficiently accurate to be taken as a guide. On the first day 200 to 300 mgm. are given. On the second day 200 mgm. On the third day the prothrombin time is estimated. If it has risen more than 50 per cent. no drug is given on that day. If less, 200 mgm. are administered, and so on for the length of the course. It must be borne in mind that there is also a withdrawal lag, *i.e.* an interval of two to ten days after cessation of administration before the prothrombin time returns to normal.

Over-dosage. Signs of over-dosage are likely to arise if the prothrombin time exceeds 80–100 per cent. of pre-treatment level. The earliest symptoms are lassitude, malaise, and severe aching in the region of the costo-vertebral articulations. Ecchymosis, hæmaturia, bleeding gums, submucous hæmorrhages, hæmarthrosis, and more dangerous complications from involvement of the brain, or viscera may then arise.

Antidote. The treatment for such complications is blood transfusion. This promptly restores the prothrombin time to normal, although a single transfusion of a pint of blood may fail to do so for more than a few hours. On the other hand, the effect may be permanent. In the former case a second transfusion is rarely necessary as there is but little tendency for fresh hæmorrhages to occur provided that the drug be discontinued. Blood must not be more than four days old because of loss of prothrombin. Vitamin K is probably valueless.

Therapeutics

The main indication for the use of dicoumarin is the prevention of intravascular **thrombosis** or its limitation if it has already developed. It has been used chiefly in an attempt to prevent post-operative **pulmonary embolism** especially in cases of extensive gynæcological operations. The prophylactic dose suggested by Butsch and Stewart is 300 mgm. on two mornings immediately preceding the morning of the operation. It must be clear, however, that a certain danger exists in operating on a patient whose coagulation time may already be lengthening. Allen and his colleagues with a wide experience of the clinical use of the drug in about 400 cases recommend prophylactic treatment to start on the day after the operation. Although it is possible that thrombophlebitis starts whilst the patient is yet unconscious under the anæsthetic, yet the development of a potential embolus of dangerous size probably takes some days. The giving of dicoumarin in this manner is, therefore, justified, but clearly allows a risk of embolism. Probably the safest method is to give the drug first on the morning of the day of operation, then within forty-eight hours it is likely that the prothrombin time will be lengthened, but this will occur too late to give rise to hæmorrhage at or soon after operation. Further administration must be regulated by prothrombin time estimations. The drug may be discontinued when the patient first sits out of bed.

Apart from prophylaxis dicoumarin may be given where pulmonary embolism has developed. The probability of a further embolism is about 30 per cent. and of a fatal one 18 per cent. Prompt use of an anticoagulant is thus indicated. Here the time lag of dicoumarin action has to be considered and it must be clear that whenever evidence of thrombophelebitis has arisen then the quicker an anticoagulant action can be obtained the greater will be the safety of the patient. In short, in all such circumstances heparin and dicoumarin should be given simultaneously. The former does not influence prothrombin time so that as soon as this reaches effective level heparin may be stopped. When it is impracticable to give heparin by intravenous drip, from 50 to 100 mgm. may be given intravenously six-hourly for the first two days. The dose for the intravenous injection of disodium dicoumarin is 5 mgm. per kilo., but it has no more rapid effect than when given by mouth and should be reserved for the rare instances when oral administration is impossible. Dicoumarin must be given for ten days after the onset of embolism or phlebitis.

Other indications for its use are **phlebitis** (post-operative or otherwise), **thrombophlebitis migrans, thrombo-angiitis obliterans,** and **coronary thrombosis, retinal thrombosis,** and possibly other vascular disorders, *e.g.* in diabetes until controlled with insulin. In these cases, although clotting has occurred the use of dicoumarin is justified in the hope of preventing extension of the initial clot. In thrombo-angiitis obliterans a maintenance dose can be arrived at (usually 100 mgm. per diem) after careful watch on the prothrombin time for two to three weeks.

There is impressive evidence of its value in preventing post-operative phlebitis and embolism.

Contraindications. 1. Hæmorrhage.

2. Subacute or acute bacterial endocarditis because of the already strong tendency to bleed and the renal damage.

3. Renal disease because the response to dicoumarin is excessive (this applies also to heparin).

4. When the prothrombin time is already prolonged, *e.g.* obstructive jaundice and severe liver disease.

5. High fever. Must be used with caution because pyrexia increases susceptibility to dicoumarin action.

GROUP XXXV

ANTIBIOTICS

Penicillin and Streptomycin

Penicillinum (B.P.). The sodium or calcium salt of the antibacterial substance produced by *Penicillium notatum.* The genus *Penicillium* owes its name to the resemblance of its fruiting body to a pencil or brush.

CHARACTERS. Pale yellow powder, hygroscopic, containing not less than 900 Units per mg.

Dose. According to the need of the patient.

The dose is now expressed in International Units. The unit contains 0·0006 mgm. of pure sodium penicillin II, maintained as a standard at the National Institute of Medical Research.

Preparations (**B.P.**)

1. **Cremor Penicillini.** 500 Units per G. of Na or Ca salt.

2. **Cremor Penicillini Sterilisatus.** 500 Units per G. of Na or Ca salt.

3. **Injectio Penicillini.** 50,000 Units per ml. of either salt.

4. **Injectio Penicillini Oleosa.** 125,000 Units of Ca salt per ml., in white beeswax and arachis oil, or ethyl oleate.

5. **Oculentum Penicillini.** 1000 Units per G. of the Ca salt.

6. **Trochisci Penicillini.** 500 Units of the Ca salt in each.

7. **Unguentum Penicillini.** The Ca salt in Ointment of Wood Alcohols ; 500 Units per G.

Historical. The mould spores are very common in the air and therefore readily contaminate culture plates. This happened in 1928 to a staphylococcal culture on which Fleming was working. He noticed that the previously vigorous staphylococcal colonies were, in the neighbourhood of the mould, fading away. Fleming, realizing the possible importance of this, made subcultures of the mould and investigated the properties of the antibacterial substance. He found it was readily diffusible in agar and a strong inhibitor of pyogenic cocci, but not of the typhoid-coli group, the influenza-pertussis group, or of the organism of plague. It was also observed that the substance was non-toxic to animals and to human leucocytes. At this time only crude penicillin was available, and it was too unstable and weak for therapeutic use.

More than a decade later Florey, working with subcultures of the original strain of Fleming's mould, succeeded in obtaining highly purified preparations of penicillin capable of preventing the growth of staphylococci and streptococci at dilutions of between 1 : 50,000,000 and 1 : 100,000,000. The range of activity against microbes was found to be extended beyond that mentioned earlier.

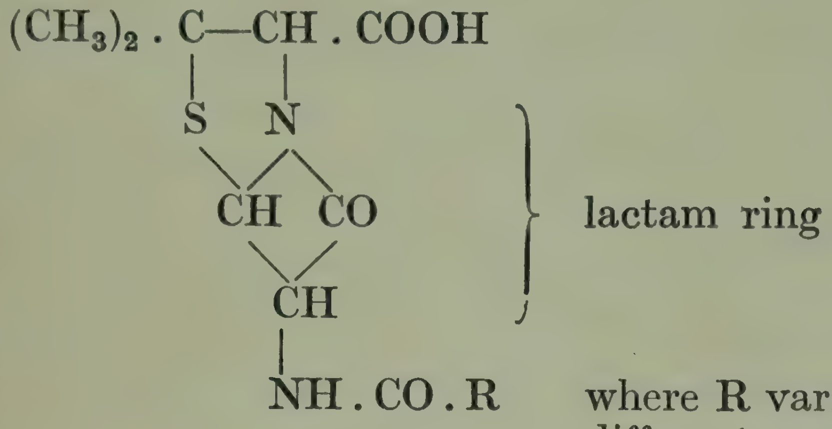
Action

Penicillin is bacteriostatic and also bactericidal though chiefly the former, to Gram-positive organisms, namely *Staphylococcus*, *Pneumococcus*, *Streptococcus pyogenes* (most *Str. viridans* are sensitive) ; *Spirillum minus*, spirochætes of syphilis, Vincent's angina, yaws, relapsing fever, and Weil's disease ; the gas-gangrene group, *Cl. œdematiens* (sulphonamide-resistant), and *Cl. welchii* ; *M. catarrhalis* ; *B. anthracis* ; Actinomyces and *C. diphtheriæ*. Although Gram-negative the gonococcus and meningococcus are fully susceptible.

The typhoid-paratyphoid-dysentery-coli group, *Str. fæcalis*, Friedlander's bacillus, *B. pertussis*, Pfeiffer's bacillus, *B. pyocyaneus* and *proteus*, *Brucella*, *B. pestis*, most viruses and tubercle bacillus are insensitive to penicillin.

Properties. Penicillin is an unstable acid. The preparations in use are the salts of sodium or of calcium which are stable between pH 5 and pH 7. The former are employed for parenteral administration, the latter for local application. The pure crystalline sodium salt of penicillin II contains 5000 units in 3 mg.

Research has revealed that there are several penicillins, four of which have been obtained in a pure crystalline state. The basic structural formula is :—



where R varies in the different penicillins.

The B-lactam ring is easily opened by alkalis and penicillinase (produced by certain bacteria) and such a change renders the penicillin inert.

Penicillin is destroyed by acids, alkalies, boiling, heavy metals, oxidizing agents and enzymes from any common bacteria. It is entirely non-toxic and is not inhibited by blood, pus, or tissue fluids. The number of bacteria has little if any effect on its action. It is highly soluble and rapidly absorbed after injection. Oral administration results in much of the drug being destroyed by the acid in the stomach. Large doses, however, *e.g.* 100,000 units, may result in an effective blood concentration, especially in achlorhydrics. The simultaneous administration of alkali inactivates penicillin even more quickly than does weak acid. As compared with intramuscular injection, quarter the amount may be excreted in the urine after oral administration in water, and half if given in egg-white. By rectum it is inactivated by penicillinase, an enzyme which is produced by various penicillin-resistant bacteria including *B. coli*. This explains why symptoms due to rapid unopposed multiplication of this organism may occur in patients under treatment with penicillin. Thus a pure growth of *B. coli* has been obtained from the sputum of bronchiectatics treated by inhalation, and from the urine of others treated by injection of penicillin for a streptococcal infection. Furthermore, sepsis at the site of the injections is usually due to coliform organisms. It is best given intravenously, intramuscularly, or when possible applied locally. Some pain is produced at the site of injection and this is most marked after the less potent preparations. The irritation is probably largely, if not entirely, due to impurities.

Storage. The dry powder retains its properties from one to two months if kept in the dark. Solutions and creams are active for about one month if kept at 3° C.

Distribution and Excretion. Penicillin is diffused widely throughout the body but appears in only minute quantities in the cerebrospinal fluid, lachrymal secretion and pancreatic juice. About 60 per cent. is excreted in the urine and some, possibly 10 per cent., in the bile in which it appears in higher concentration than in the blood. The remainder cannot be recovered and may be destroyed in the body.

Excretion is so rapid that the blood concentration falls steeply and thus renders the maintenance of a therapeutic level of at least 0·05 Units per ml. beyond 3 hours a matter of difficulty. The duration of effective concentration is not proportional to the dose, thus 10,000 units may be adequate for 2 hours, yet 100,000 units will be effective for only 4 hours.

The greater part of penicillin injected appears in the urine in the first hour. In certain renal diseases, *e.g.* nephritis, the output of penicillin is delayed and the blood concentration is maintained at effective levels for longer periods.

Therapeutics

Local. Penicillin may be administered by inhalation in the form of an ærosol. The watery solution contains 25,000 units per c.cm. The ærosol is inhaled through the mouth for half-an-hour, thus providing a sessional-dose of about 100,000 units. Treatment should consist of at least two sessions a day for a period of ten days. The penicillin-sensitive organisms rapidly disappear from the sputum, but coliform organisms increase greatly in number. This does not appear to be harmful as a rule, but *coli* bacillæmia and pyelitis have been reported. The inhalation treatment is of great value in non-suppurative **bronchitis** and bronchitic asthma. It is of little use in bronchiectasis, and useless in lobar pneumonia. It is also of value in the treatment of infections of the upper respiratory tract. Penicillin is available as a calcium salt in powder form. The potency of various samples is very variable, *e.g.* 7 to 160 units per mgm. The calcium salt may be applied in aqueous solution, as an emulsion cream made with Lanette wax, vaseline and water, or as a powder mixed with sulphanilamide which proves to be a satisfactory diluent. **Conjunctivitis** and **corneal ulcers** associated with penicillin-sensitive bacteria are treated with eye-drops of the solution. Superficial **burns** are treated with the cream or powder applied every twenty-four hours. **Vincent's angina** is treated with the lozenges and parenteral administration. **Wounds** may be treated likewise after the elimination of pockets and dead tissue. Penicillin has no adverse effects on skin-grafts. Sinuses, cavities, and infected joints are treated with the solution. The more loculated the cavity, the more disappointing is the result.

Good results have been reported in the treatment of **sycosis barbæ** with the cream.

General. Owing to the rapid excretion it is difficult to maintain a blood concentration at effective level. In view of this fact *it should not be given for conditions amenable to sulphonamide treatment.*

Continuous Intravenous Drip. It is usual to give sodium penicillin, 30,000 units in 1 pint of sterile saline in six hours. Calcium penicillin has also been used in this manner without harm. The advantage of the method is that it does not disturb the patient and is painless. The disadvantage is that thrombophlebitis is apt to occur, on the average after 100 hours. Administration by this route must then cease.

Intermittent Intramuscular Injection. 15,000 units in 2 c.cm. sterile water are given into the vastus lateralis. This has the advantage of simplicity, but the disadvantages of disturbance, pain, and fluctuations of blood titre.

Continuous Intramuscular Drip. The same dose as for intravenous drip. If leakage around the needle occurs, or if œdema of the limb arises, the volume should be reduced to 2 pints daily, and the limb is elevated. Local abscesses may form.

Intramuscular Oil-wax Suspension. This preparation is given in order to provide slow absorption over a long period. The injection is given twice a day. It is useful in certain chronic infections and in debilitated "needle-shy" patients. It is, however, painful.

Intramuscular Procaine Penicillin. Procaine penicillin is a compound in which the anæsthetic action of procaine is lost. Penicillin is slowly liberated and thus an effective blood content may be obtained from one injection daily. Each mil. of arachis oil contains 300,000 units penicillin and the equivalent of 120 mg. of procaine base.

Intrathecal Injection. Owing to a highly selective blood-brain barrier penicillin, as compared with the sulphonamides, fails to pass in appreciable amount into the cerebrospinal fluid. In cases of meningitis it must, therefore, be introduced by lumbar puncture. To reduce the likelihood of plastic meningitis arising from impurities the strength should seldom exceed 1000 units in 1 c.cm From 5000 to 10,000 units may be thus administered. The blood-brain barrier has this advantage that the penicillin persists in effective concentration much longer in the C.S.F. than it does in the blood, in fact, 5000 units will be effective for twenty-four hours. The dose is repeated daily. If the case has come late for treatment, or if lumbar administration does not produce prompt relief, it may be necessary to give penicillin also into the cisterna magna and into the lateral ventricles.

In cases of **pneumococcal** and **streptococcal septicæmia**, if sulphonamide-resistant, 15,000 units are given parenterally every three hours.

It is the drug of choice for **staphylococcal septicæmia.**

In **diphtheria** penicillin appears to be of distinct value, although the results are less dramatic than in many other diseases. This is so because the organisms are more or less isolated from the circulation and the harmful effects are due to the toxin elaborated. The daily dose by the usual method of intramuscular injection should be 200,000 units in three-hourly fractions. This may be combined with a penicillin spray for local application, and must be also accompanied by the administration of antitoxin.

In the case of **abscesses** and **wounds** with sloughs and deep crevices, **gas-gangrene** and **osteomyelitis,** the local application will fail, but the injection of 100,000 to 300,000 units three-hourly will result in the shedding of slough and will then allow of local treatment with penicillin and sulphonamide.

Under systemic treatment compound **fractures** can be closed in spite of the fact that they are always infected.

Penicillin cures **gonorrhœa** rapidly. It is especially valuable in the sulphonamide-resistant forms. The suggested dose is 10,000 units intramuscularly every two hours for ten doses, or 100,000 units in the morning and 50,000 units at night, in oil-wax suspension.

Urinary infection with susceptible organisms responds well to relatively small doses because of the concentration of penicillin by the kidneys in the process of excretion.

Reference to the list of penicillin-sensitive organisms given above will indicate the diseases in which this drug will probably be of value.

In **meningitis** due to sulphonamide-resistant organisms and in all pneumococcal and staphylococcal cases penicillin should be given intrathecally on the lines described above in doses of 10,000 units daily and 150,000 units in wax suspension intramuscularly twice a day.

The treatment of **gas gangrene** combined with surgery has been effective.

The results of treatment of **bacterial endocarditis** are very encouraging. The initial dose is 500,000 units daily. If pyrexia persists for more than five days the dose should be raised by 50 per cent. and so on. In some cases 20 million units daily are needed. The length of treatment is at least four weeks.

Spirochætes rapidly disappear from the primary lesions of **syphilis** if treated with penicillin. All stages of the disease respond favourably to the drug except neurosyphilis. It is doubtful whether cure can be effected. 500,000 units daily for 13 days should be given, and 14 injections of 0·06 grm. mapharside over 20 days.

The intrathecal administration of penicillin is apt to be followed by a plastic meningeal reaction to the irritant properties of the impurities. The dilution should be higher than for the intramuscular route.

General effects of treatment. The first signs of benefit arising from the use of penicillin in acute infections are improvement in the pulse, colour, appetite, and sleep. Pyrexia may continue for several days or weeks whilst the lesion is healing. It is important to remember this because the response is thus unlike that due to successful sulphonamide therapy. Occasionally an urticarial rash occurs during treatment. It responds well to anti-histamine drugs (*q.v.*). In some individuals a scaly rash resembling seborrhœic eczema appears on the forehead, neck and arms. In syphilis penicillin may invoke a Jarisch-Herxheimer reaction.

Streptomycin

SOURCE. A product of growth of the soil organism *Actinomyces griseus.*

CHARACTERS. Stable white powder soluble in water. Liable to lose potency unless stored at temperatures of less than 15° C.

ASSAY. A unit is the amount which will inhibit the growth of *B. coli* in 1 c.c. of broth. 1 unit = 1 microgramme (1/1000 mgm.).

Dose. 500,000 units (0·5 grm.) by intramuscular injection.

Action and Uses

The therapeutic use of this drug is still in its experimental stage. It differs from penicillin notably in the fact that it inhibits in high dilution many Gram-negative organisms, especially *B. coli*, *B. tularense*, *B. dysenteriæ* and salmonella.

It also inhibits *M. tuberculosis* in 1 in 200,000 dilution, and *H. influenzæ*.

In meningitis it does pass the blood-brain barrier. It may be given by mouth if it is desired to reduce the intestinal flora prior to operation on the intestines.

It has proved of value in tularæmia, *B. coli* pyelitis, influenzal meningitis and brucellosis.

Many cases of acute tuberculosis in human beings have been cured by its use. Even tuberculous meningitis may respond to intramuscular injections of 0·5 G. four times daily.

Toxic effects are fever, pains in the limbs, flushing, tinnitus, deafness and giddiness.

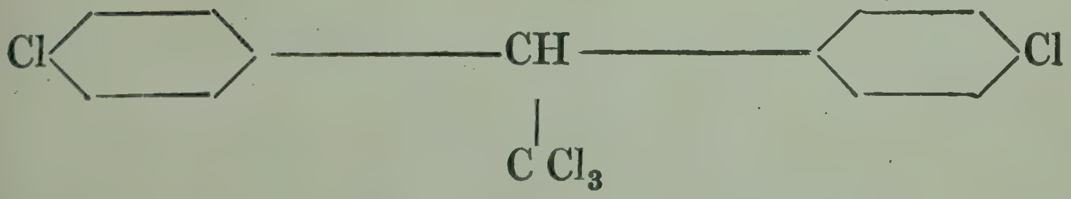
Streptomycin-resistant tubercle bacilli develop from 6 to 12 weeks after commencing treatment. This resistance may be enormous and is not lost by subsequent generations of bacteria.

GROUP XXXVI

Insecticides

The destruction of disease-bearing insects, notably mosquitoes, body-lice, fleas and the common fly, has until recently presented great difficulties because the toxic nature of the insecticides has rendered them unsuitable for use on the human body or in dwelling-houses. Thus nicotine is highly toxic and derris may produce unpleasant symptoms if inhaled. Pyrethrum, which is obtained from the flowers of *Chrysanthemum cineariæfolium*, is a powerful and rapidly acting insecticide and repellant. Kerosene extracts are used as fly-sprays and mosquito larvicides. The ointment containing 0·75 per cent. of pyrethrins has been used in treating scabies. Pyrethrum suffers the disadvantage of losing its insecticidal properties rather rapidly when exposed to sunlight. It does, however, destroy insects more rapidly than D.D.T.

D.D.T. is dichlordiphenyltrichlorethane.



It loses its insecticide properties if either of the terminal chlorines is moved to the *ortho* position.

Characters. Colourless, crystalline solid, sparingly soluble in water; more soluble in organic solvents, *e.g.* alcohol and kerosene. Faint sweetish odour; almost tasteless. Very stable.

Percentage Preparations. In the form of a powder made with any inert material, 5 to 10 per cent. This is applied to clothes, furniture and the human body.

In the form of a solution in kerosene 0·5 to 3 per cent. This is sprayed on walls, ceilings and clothes as a fairly coarse spray to encourage deposition.

In the form of distemper or paint, D.D.T. may be incorporated in 2 per cent. concentration. This aims at rendering the walls and ceilings lethal to insects for several months. The D.D.T. paints are less effective than is repeated spraying because much of the substance lies below the surface of the paint and will have no effect on insects walking over the walls. The application of a thin oil-emulsion, 0·1 G. D.D.T. per square foot of wall, will prove lethal to mosquitoes and flies for three months.

Action

The drug is absorbed through the feet or body of the insect and kills by its action on the nervous system. It causes hyperexcitability, tremors, convulsions and finally paralysis. Death may not occur for some hours, and seldom in less than five minutes. The speed of destruction depends upon the concentration and the vehicle, powders killing more slowly than solutions.

D.D.T. as ordinarily used is non-toxic to human-beings because it is absorbed through the skin with great difficulty. The powder can be taken by mouth in relatively large doses without effect. When in a solvent such as acetone, kerosene, or oils, its repeated application in high concentration may give rise to signs of poisoning. These are nervousness, twitching, insomnia, headache, aching limbs and general malaise. Recovery may take some weeks. Convulsions, coma, depression of the respiratory centre and death with pulmonary œdema have been reported in a case of poisoning from D.D.T. taken in solution by mouth. The lethal dose is about 150 mgm. per kilo of body-weight. Experimental poisoning in animals has shown that the most striking changes are to be found in the liver and kidneys. The former exhibits centrolobular necrosis and fatty degeneration; the kidneys show tubular necrosis.

The symptoms of poisoning resemble those of carbon tetrachloride. It has been suggested, therefore, that they should be treated with intravenous calcium gluconate, 20 mils of 10 per cent.

Uses

D.D.T. is used chiefly in the forms mentioned above for the destruction of insects which transmit disease. A 2 per cent. D.D.T. emulsion applied to the hair is used in **pediculosis.** It kills pediculi in an hour and persists long enough to destroy the larvæ. Impregnation of underwear, 2 per cent. by weight of the garment, gives valuable protection which will persist in spite of repeated washing in soap and water. Dry cleaning removes the D.D.T. Its most dramatic success has been the control of **typhus** epidemics during the last war.

APPENDIX

A LIST OF LATIN PHRASES COMMONLY USED IN THE WRITING OF PRESCRIPTIONS

aa.	Ana	of each.
Ad.	Adde	add.
Ad lib.	Ad libitum	to the desired amount.
Ad us.	Ad usum	according to custom.
Æq.	Æquales	equal.
Aq.	Aqua	water.
Aq. bull.	Aqua bulliens	boiling water.
Aq. dest.	Aqua destillata	distilled water.
Bib.	Bibe	drink.
Bis ind.	Bis indies	twice a day.
Bis in 7 d.	Bis in septem diebus	twice a week.
C.	Cum	with.
Cap.	Capiat	let him take.
C. m.	Cras mane	to-morrow morning.
C. m. s.	Cras mane sumendus	to be taken to-morrow morning.
C. n.	Cras nocte	to-morrow night.
Cochl.	Cochleare	spoonful.
Cochl. ampl.	Cochleare amplum	a table-spoonful.
Cochl. infant.	Cochleare infantis	a tea-spoonful.
Cochl. mag.	Cochleare magnum	a table-spoonful.
Cochl. mod.	Cochleare modicum	a dessert-spoonful.
Cochl. parv.	Cochleare parvum	a tea-spoonful.
Contin.	Continuetur	let it be continued.
Cuj.	Cujus	of which.
C. v.	Cras vespere	to-morrow evening.
Cyath	Cyathus	a glassful.
Cyath. vinos.	Cyathus vinosus	a wine-glassful.
D.	Dosis	a dose.
d.	Da	give.
D. d. in d.	De die in diem	from day to day.
Det.	Detur	let it be given.
Dieb. alt.	Diebus alternis	on alternate days.
Dim.	Dimidius	one half.
Div.	Divide	divide.
D. in p. æ.	Divide in partes æquales	divide into equal parts.
Exhib.	Exhibeatur	let it be given.
F. or ft.	Fiat	let it be made.
F. h.	Fiat haustus	make a draught.
F. m.	Fiat mistura	make a mixture.
F. pil.	Fiat pilula	make a pill.
Gutt.	Gutta or guttæ	drop or drops.
Habt.	Habeat	let him have.
Hor. intermed.	Horis intermediis	at intermediate hours.
H. s.	Horâ somni	at bedtime.
Ind.	Indies	daily.
Lat. dol.	Lateri dolenti	to the painful side.
Mit.	Mitte	send.
Mod. præscript.	Modo præscripto	in the manner directed.
Oct. pars	Octava pars	an eighth part.
O. m.	Omni mane	every morning.
Omn. bih.	Omni bihorâ	every two hours.
Omn. hor	Omni horâ	every hour.
O. n.	Omni nocte	every night.
P. or pt.	Perstatur	continue.
Part. æq.	Partes æquales	equal parts
P. r. n.	Pro re natâ	when required.
Q. l.	Quantum libet	as much as is requisite.
Q. s.	Quantum sufficit	a sufficient quantity.
Q. v.	Quantum volueris	at will.
Quart. pars	Quarta pars	a quarter.
R.	Recipe	take.
Rep.	Repetatur	let it be repeated.
Sing.	Singulorum	of each.
Sum.	Sumat or sumendum	let him take or let it be taken.
T. d.	Ter in die	three times a day.
T. e quat. part.	Tres e quattuor partibus	three quarters.

INDEX

ABBREVIATIONS, 33, 34
Abortion, lead in, 368, 370
— progesterone in, 448
Abscess, penicillin therapy for, 503
Acacia, 39
Aceta, 10
Acetanilidum, 296, 298
Acetarsol, 408
Acetarsone, 408
Acetates, 153
Acetic acid, 163
Acetomenaphthonum, 486
Acetphenetidin, 298
Acetum scillæ, 342
Acetyl-β-methylcholine chloride, 288
Acetyl-choline, 223, 287
— hydrochloride, 287
Acetyl - salicylic acid, 296, 309
Achalasia of œsophagus, amyl nitrite in, 293
Acidosis, sodium bicarbonate in, 152
Acid quinine hydrochloride, 302
Acids, 162
— toxicology of, 167
Acidum aceticum, 163
— — glaciale, 163
— acetylsalicylicum, 309
— arseniosum, 405
— ascorbicum, 481
— benzoicum, 314
— boricum, 132
— citricum, 163
— hydrochloricum, 162
— hydrocyanicum dilutum, 351
— hypophosphorosum dilutum, 163
— lacticum, 164
— mandelicum, 168
— nicotinicum, 479
— nitricum, 162
— oleicum, 44
— phosphoricum, 162
— ricinoleicum, 85
— salicylicum, 309
Acidum sulphuricum, 162
— — aromaticum, 162
— sulphurosum, 124
— tannicum, 98
— tartaricum, 164
— trichloraceticum, 163
Acne, œstrogens in, 447
Aconite, 281
— toxicology of, 284
Aconitina, 282
Acriflavina, 121
Acromegaly, œstrogen therapy in, 447
Actinomycosis, sulphonamides in, 333
Adalin, 221
Addison's disease, adrenal cortical hormone in, 435
— — salt in treatment of, 146, 435
Adeps, 40
— benzoinatus, 40, 314
— lanæ, 40
— — hydrosus, 40
Adrenal gland, 431, 434
Adrenalina, 431
Adrenergic nerves, 224
Adrenocorticotrophic hormone, 440
Æthanolamina, 44
Æther, 198
Æthisteronum, 449
Æthylenum, 201
Æthylis chloridum, 200
Agar-agar, 77
Agotan, 356
Agranulocytosis,
  amidopyrine and, 300
  gold salts and, 374
  sulphonamides and, 328
  thiouracil and, 429
Albucid, 318
Alcohol, benzylicum, 190
— cetostearylicum, 190
— ethyl, 184
— methyl, 190
— tertiary amyl, 221
— toxicology of, 190
— tribromœthyl, 190

Alcoholia lanæ, 40
Aldehydes, 205, 210
Aliphatic narcotics, 204
Alkaloids, definition of, 2
Almonds, 45
Aloes, 89
Aloinum, 89
Alum, precipitated toxoid, 462
— purified, 380
Alumen, 380
Aluminii hydroxidum, 380
Aluminium, 380
Ambinon, 438, 439
Amenorrhœa, œstrogen therapy in, 446
American wormseed oil, 109
Amethocainæ hydrochloricum, 281
Amidopyrine, 299
— and barbiturates, 214
Aminacrinæ hydrochloridum, 121
Aminoacridine hydrochloride, monohydrate, 121
Aminophylline, 260
Ammoniæ fortis, liquor, 153
Ammoniated mercury, 39I
Ammonii acetatis, liquor, 154
— benzoas, 314
— bicarbonas, 153
— bromidum, 178
— chloridum, 154
— mandelas, 168
Ammonio-mercuric chloride, 396
Ammonium, 153
— benzoate, 314
— bicarbonate, 153
— bromide, 178
— chloride, 154
— ichthosulphonate, 134
— mandelate, 168
Amœbiasis, iodoxyquinoline derivatives used in, 348
Amphetaminæ sulphas, 459
Amphetamine, 459
Ampullæ, 24
Amygdala amara, 45
— dulcis, 45
Amygdalin, 353
Amyl nitrite, 291
Amylene hydrate, 221
Amylis nitris, 292
Amylum, 40
Amytal, 217
Anacardone, 62
Anæmia, folic acid in, 481
— iron therapy in, 387
— pernicious, liver or stomach therapy in, 388, 457
Anæsthesine, 279
Anæsthetics, 181
— basal, 217
— general, 181
Anahæmin, 456
Analeptics, 62
Analgesics, 215, 238
Anaphrodisiacs, 225
Anatoxin, 462
Androgens, 450
Anethaine, 281
Anethum, 71
Aneurinæ hydrochloridum, 476
Angina pectoris, aminophylline in, 261
— — amyl nitrite in, 293
— — nitroglycerin in, 294
Anhydro-glucochloral, 209
Anhydrous lanolin, 40
— sodium phosphate, 83
Anise, 70
Anthelmintics, 103
Anthisan, 365
Anthracene purgatives, 77, 86
Antianthrax serum, 467
Antibiotics, 497
Anticoagulants, 488
Antifebrin, 296, 298
Antihistamine substances, 365
Antimeasles serum, 466
Antimonii et potassii tartras, 413
— et sodii tartras, 414
Antimony, tartarated, 413
Antimonyl sodium tartrate, 414
Antiphlogistine, 381
Antiplague serum, 466
— vaccine, 472
Antipyretics, 295, 311
— toxicology of, 301
Antipyrin, 296, 298

Antirachitic vitamin, 485
Antiscorbutic vitamin, 482
Antiseptics, 111, 392
— urinary, 74, 133, 311
Antistine, 365
Antitoxic sera and toxins, 460
Antitoxin, gas-gangrene, 466
Antitoxinum diphthericum, 461
— œdematiens, 466, 467
— septicum, 466
— tetanicum, 463
— Welchicum, 467
Anti-typhoid-paratyphoid vaccine, 472
Antivenene, 466
Antostab, 439
Antoxylin-S., 439
Antrypol, 147
Antuitrin growth, 439
Antuitrin-S., 439
Aperients, 84
Aphrodisiacs, 225
Apiol, 56
Apomorphine, 344
— hydrochloride, 242
Aqua anethi concentrata, 72
— aromaticæ, 10
— calcis, 157
— camphoræ, 60
— chloroformi, 192
— cinnamomi concentrata, 68
— destillata, 10, 142
— menthæ piperitæ, 70
— pro injectione, 142
Arachis oil, 45
Argenti nitras, 370
— — induratus, 370
Argentoproteinum, 370
Argentum, 370
Argyria, 371
Argyrol, 371
Arsamin, 408
Arseni trioxidum, 405
Arsenic, 405
— toxicology of, 412
Arsenical keratosis, 413
Arsenicals, pentavalent, 408
— trivalent, 410
Arsenious acid, 405
Arsenium, 405
Arsenobenzol, 410
Arsenobillon, 410
Arsphenamine, 410
— silver, 410
Arthritis, thyroid therapy in, 426
Ascaridole, 109
Ascorbic acid, 481
Asphyxia, oxygen in, 172
Aspirin, 296, 309
— calcium, 313
Asthma, adrenaline in, 433
— aminophylline in, 261
— belladonna in, 251
— cigarettes, 254
— ephedrine in, 458
— nitrates in, 156
— nitrites in, 293
— papers, 293
— pethidine in, 238
— stramonium in, 254
Astringents, 96
Atebrin, 307
Atophan, 356
Atoxyl, 408
Atropine, 224, 236, 244
— methylnitrate, 250
— sulphate, 244
Aurantii cortex recens, 54
— — siccatus, 54
Auricular fibrillation, digitalis in, 339
— — quinidine in, 305
— flutter, digitalis in, 340
Auri et sodii thiosulphas, 372
Aurum, 372
Avertin, 190

BACTERIAL endocarditis, heparin in, 492
— — penicillin therapy in, 503
B.A.L., 413
Balsam of Peru, 73
— of Tolu, 73
Balsams, definition of, 5
Balsamum Peruvianum, 73
— Tolutanum, 73
Barbital, soluble, 212
Barbitone, 212
Barbitonum sodium, 213

Barbiturates, toxicology of, 221
Barii chloridum, 161
— sulphas, 161
Barium, 161
— chloride, 161
— sulphate, 161
— sulphide, 161
— toxicology of, 161
Baryta sulphurata, 161
Baths, 142
Bayer 205, 147, 489
B.C.G. vaccine, 471
Bedsores, alcohol applications as preventative of, 188
Beeswax, 42
Belladonna, toxicology of, 252
Belladonnæ folium, 243
— herba, 243
— radix, 244
Bellergal, 364
Benadryl, 365
Benzedrine, 459
— sulphate, 459
Benzene, 121
Benzidine-heparin, 490
Benzoated lard, 314
Benzocaina, 279
Benzoic acid, 314
Benzoin, 314
Benztrone, 443
Benzyl-benzoas, 316
Benzyl-sulphanilamide, 318
Beprochin, 307
Beri-beri, vitamin B and, 477
Betanaphthol, 118
Betel, 72
Bhang, 241
Bile, 101
Bilharziasis, stibophenum in, 416
— tartar emetic in, 415
Biological assay, 7
Bismarsen, 405
Bismuth, 402
— arsphenamine, 405
— carbonate, 402
— oxycarbonate, 402
— oxychloride, 403
— oxygallate, 403
— precipitated, 402
Bismuth, salicylate, 402
— sodium tartrate, 403
— stovarsol, 405
— subcarbonate, 402
— subchloride, 403
— subsalicylate, 402
Bismuthi carbonas, 402
— et sodii tartras, 403
— oxychloridum, 403
— præcipitatum, 402
— salicylas, 402
— subgallas, 403
Bistovol, 405
Bitter almond, 45
Bitters, 52
Black draught, 80, 87
Blaud's pill, 382
Bleaching powder, 124
Blood transfusion, heparin in, 491
Blue ointment, 390
— pill, 390
— vitriol, 377
Bluestone, 377
Boils, magnesium salts and glycerin in, 47, 82
— sulphonamides in, 334
Boracic acid, 132
Borax, 132
Boric acid, 132
Botulinus antitoxin, 467
Bougies, 24
Brassfounders' ague, 376
Brilliant green, 122
British Pharmaceutical Codex, 2
— Pharmacopœia, 2
Bromethol, 190
Bromides, 177
Bromism, 179
Bromoformum, 180
Bronchitis, iodides in, 174
— ipecacuanha in, 349
— penicillin in, 501
Brucellosis, streptomycin in, 505
— sulphonamides in, 332
Brucine, 261, 264
Buginaria, 24
Burns, carron oil in, 159
— chlorbutol in, 209

Burns, gentian violet in, 122
— penicillin in, 501
— sulphonamides in, 335
— tannic acid in, 98
— triple dye in, 122
Butacainæ sulphas, 280
Butolan, 110
Butyl-chloral hydrate, 208
Butylis aminobenzoas, 280

CACAO butter, 138
Cachets, 24
Cade, oil of, 59
Caffeina et sodii benzoas, 257
Caffeine, 257
Cajuput oil, 65
Calabar bean, 289
Calamine, 375
Calciferol, 482
Calcii carbonas, 157
— chloridum, 157
— — hydratum, 157
— gluconas, 157
— hydroxidum, 157
— lactas, 158
— mandelas, 169
— phosphas, 157
Calcium, 156
— aspirin, 313
— aurothiomalate, 373
— carbonate, precipitated, 157
— chloride, 157
— — hydrated, 157
— gluconate, 157
— hydroxide, 157
— lactate, 158
— mandelate, 169
— phosphate, 157
Calomel, 391, 398
Calumba, 53
Calx, chlorinata, 124
— sodica, 158
Camphor, 60
Camphorated oil, 60
Cannabis, 240
Cantharidin, 55
Capsicum, 68
Capsules, 25
Caraway fruit, 71
Carbachol, 288
Carbamates, 205, 212
Carbamylcholine chloride, 288
Carbarsone, 408
Carbo, 169
— activatus, 169
Carbohydrate nutrients, 48
Carbolic acid, 113
Carbon dioxide, 170
— tetrachloride, 107
Carbonates, 149
Carbonei dioxidum, 170
Carbromalum, 221
Carcinoma of prostate, œstrogens in, 447
Cardamomum, 69
Cardiazol, 62
Cardophylin, 260
Carminative action of volatile oils, 56
Carotene, 475
Carron oil, 159
Carum, 71
Caryophyllum, 67
Cascara sagrada, 88
Castor oil, 77, 84
Cataphoresis, 27
Catechu, 99
Caustic potash, 148
— toughened, 370
Cellulose, 77
Cera alba, 42
— emulsificans, 42
— flava, 42
Cerata, 25
Cerebrospinal fever, sulphonamides in, 330
Cevitamic acid, 481
Chalk, precipitated, 157
— prepared, 156
Chancroid, sulphonamides in, 332
Charas, 240
Charcoal, 169
Chaulmoogra oil, 135
Cheilosis, lack of riboflavin causing, 480
Chenopodium, 109
Cherry, wild, syrup of, 354
Chilblains, calcium in, 161
— histamine in, 365
Chillie paste, 69

Chiniofonum, 348
Chloral formamide, 209
— hydrate, 206
— — toxicology of, 208
Chloralamide, 209
Chloralis hydras, 206
Chloralose, 209
Chloramina, 125
Chloramine-T, 125
Chlorbutol, 209
Chloretone, 209
Chlorinated lime, 124
Chlorine, 124
Chlorocresol, 117
Chloroform, 192
— poisoning, delayed, 198
Chlorophyll, 389
Chloroxylenol, 118
Cholagogues, 101
Cholecystitis, fluid magnesia in, 82
— hexamine in, 133
— olive oil in, 44
— sulphonamides in, 332
Cholecystography, pheniodol in, 177
Cholera vaccine, 472
Choline, 287
— esterase, 224
Cholinergic nerves, 224
Choryl, 288
Chromii trioxidum, 417
Chromium, 417
Chrysarobin, 133
Churrus, 240
Cinchocainæ hydrochloridum, 280
Cinchona bark, 301
Cinchonidine, 301
Cinchonine, 301
Cinchonism, 304
Cinchophen, 356
Cineole, 65
Cinnamomum, 68
Cinnamon, 68
Circulation time, use of sodium dehydrocholate for determination of, 102
Citrates, 153
Citric acid, 163
Climacteric, bromides in, 180
Climacteric, œstrogenic therapy in, 446
Clinestrol, 444
Cloves, 67
Coal tar, 116, 119
Cocaine, 275
— hydrochloride, 276
— substitutes, 279
Cocamania, 279
Cocculin, 266
Coccus, 136
Cochineal, 136
Cocoa, 260
Codeine, 238
— phosphate, 239
Cod-liver oil, 484
Colchici cormus, 354
— semen, 355
Colchicina, 355
Colchicum, 354
Colic, intestinal, nitrites in, 293
Colitis, ulcerative, bismuth in, 404
Collargol, 371
Collodia, 10
Collodion, 138
Collodium flexile, 138, 198
Colloid silver, 371
Colloids, 37
Collosol, auro-calcium, 373
— manganese, 379
Collosols, 37
Collunaria, 25
Collyria, 25
Colocynth, 78, 93
Colophonium, 60
Colouring agents, 136
Colsulanyde, 318
Condy's fluid, 131
Condylomata, mercury in, 395
Confectiones, 25
Conii folium, 268
Coniine, 268
Conium, 268
Conjunctivitis, penicillin in, 501
— sulphonamide therapy in, 327
Constipation, castor oil in, 86
— fluid magnesia in, 82
— glycerin in, 47
— senna in, 88

Contact soap, 139
Copper, 377
Coramine, 62
Coriander fruit, 71
Coriandrum, 71
Cornea, affections of, lack of riboflavin and, 480
Corneal ulcers, penicillin in, 501
Corpus luteum hormone, 448
Corrosive sublimate, 390
Cortin, 434
Cortiron, 434
Cotton, 137
Cottonseed oil, 45
Coughing, relief of, opium in, 233
— — pethidine in, 238
Counter-irritants, 55
Cream of magnesia, 80
Cremora, 10
Creosote, 120
Crescormone, 439
Cresol, 116
Creta, 156
Cretinism, thyroid therapy in, 425
Crisalbine, 372
Crocus, 137
Croton chloral hydrate, 208
— oil, 78, 95
Cubeba, 74
Cupri sulphas, 377
Cuprum, 377
Curare, 272
Curd soap, 139
Cushing's syndrome, œstrogens in, 447
Cusso, 105
Cyanosis due to sulphanilamide, 326
Cyclopropane, 202
Cystitis, hexamine in, 133
— mandelic acid in, 168
— sulphonamides in, 331

D.D.T., 505
Dagenan (M. & B. 693), 318
Dakin's solution, 124
Dangerous Drugs Acts, 34, 35
Deadly nightshade, 243
Decholin, 102
Decicain, 281
Dehydrocholic acid, 102
Demulcents, 38
Deoxycortoni acetas, 434
Depilatory, 161
Dermatitis herpetiformis, sulphonamides in, 333
— iron in, 386
Dermatol, 405
Dermatology, Lassar's paste in, 377
Dermatoses, pyogenic, sulphonamides in, 334
Derris, 505
Desiccated stomach, 455
Desoxycorticosterone acetate, 434
Dettol, 117
Dextrosum, 49
— hydratum, 49
Diabetes insipidus, vasopressin in, 438
— insulin in, 452
— opium in, 234
Dial, 217
Diamorphine hydrochloride, 239
Diaphoresis, opium and, 234
Diarrhœa, bismuth in, 404
— hydrochloric acid in, 166
— kaolin in, 381
— opium in, 232
Diastase, 76
Dichlorophenol-indophenol, 141
Dick test, 466
Dicodid, 239
Dicoumarol, 488, 492
Dienœstrol, 444
Diethylstilbœstrol, 444
Digestive ferments, 75
Digitalinum verum, 336
Digitalis, 335
— folium, 335
— lanata, 336
— præparata, 335
Digitoxin, 336
Digoxin, 336
Di-iodotyrosinum, 424

Dilaudid, 237
Dill fruit, 71
Dimenformon, 443
Dinitrocellulose, 137
Diodone, solution of, 175
Diodoquin, 348
Dionine, 237
Dioxyanthranol, 134
Diphenan, 110
Diphtheria antitoxin, 461
— penicillin in, 502
— prophylactic, 462
— toxin, diagnostic, 463
Disinfectants, 111
Di-sipidin, 436
Di-sodium hydrogen phosphate, 83
Dispensing, 34
Distilled water, 10, 142
Dithranol, 134
Diuretics, 57, 155, 257 *et seq.*
Diuretin, 260
Doca, 434
Dolantin, 238
Doryl, 288
Doses, 9, 27
Dover's powder, 227, 347
Drugs, administration of, modes of, 26
— incompatibility of, 30
— pharmacological and therapeutic actions of, 36
Duodenal ulcer, belladonna in, 251
— — carbonates in, 151, 159
— — hyoscyamine in, 257
— — olive oil in, 44
Dusting powders, 48
Dyes, 139
Dyschezia, glycerin in, 47
Dysentery, amœbic, acetarsol in, 409
— — carbasone in, 409
— — emetine in, 350
— bacillary, sodium sulphate in, 84
— — sulphonamides in, 332
Dysmenorrhœa, androgens in, 451
— œstrogenic therapy in, 447

Eau de Javelle, 125
E-B-I. 348
Eczema, ichthyol in, 135
Elutriation, 6
Embolism, arterial, papavarine hydrochloride in, 237
— pulmonary, dicoumarin in, 495
Emetics, 242, 343
— classification of, 344
Emetinæ et bismuthi iodidum, 348
— hydrochloridum, 348
Emollients, 40
Emplastra, 25
Emulsio olei morrhuæ, 484
Emulsiones, 11
Emulsions, definition of, 5
Encephalitis, vaccinal, 469
Endocrine glands, preparations of, 419
Enemata, 25
Enterospasm, 366
Enuresis, ephedrine in, 459
Epanutin, 216
Ephedrinæ hydrochloridum, 458
Ephedrine, 252, 457
Epilepsy, bromides in, 179
— phenobarbitone in, 216
Epinephrine, 431
Epsom salts, 80
Ergoclavine, 360
Ergometrinæ maleas, 358
Ergometrine, 358
Ergonovine maleate, 358
Ergosterol, irradiated, 482
Ergot, 357
Ergotaminæ tartras, 358
Ergotamine, 358, 363
Ergotinine, 357
Ergotism, 361
Ergotoxine, 357
Erythema multiforme, antihistamine preparations in, 366
Erythroxylum coca, 275
Eschatin, 434
Eserine salicylate, 289
Esidrone, 397
Essentiæ, 25

Essential oil, definition of, 4
Estradiol benzoate, 443
Ether, 198
Ethisterone, 449
Ethocaine hydrochloride, 280
Ethyl alcohol, 184
— aminobenzoate, 279
— carbamate, 212
— chaulmoograte, 135
— chloride, 200
— hydroxide, 184
— nitrite, 293
— oxide, 198
Ethylene, 201
Eucalyptol, 65
Eucalyptus oil, 65
Eucortone, 434
Eumydrine, 250
Euparatone, 429
Euphyllin, 260
Eusol, 126
Evipan, 219
Expectorants, 56, 343
Exsiccated ferrous sulphate, 382
Extract of malt, 50
Extracta, 11
Extractum hepatis liquidum, 455
— parathyroidei, 429
— suprarenali corticis, 434
Eye ointments, 18

Fats, definition of, 4
Fellis bovini, extractum, 101
Femergin, 358, 363
Fennel fruit, 71
Ferri carbonas saccharatus, 382
— et ammonii citras, 383
— perchloridi, liquor, 383
— sulphas, 382
— — exsiccatus, 382
Ferric chloride, solution of, 383
Ferrous sulphate, 382
Ferrum, 382
Fibrositis, aspirin in, 313
— histamine in, 365
Filix mas, 103
Fixed oils, definition of, 3
Flatulence, charcoal in, 170
Flavouring agents, 48
Flowers of sulphur, 90
Fluid magnesia, 80
Fluoresceinum sodium, 140
Foam baths, 347
Fœniculum, 71
Folic acid, 476, 481
Fomenta, 25
Formaldehyde, 123
Formalin, 123
Formol toxoid, 462
Fouadin, 416
Fowler's solution, 405
Foxglove leaves, 335
Fractures, compound, penicillin in, 503
Friars' balsam, 314
Fructose, 50
Fuller's earth, 48, 381

Galla, 98
Ganga, 240
Gardenal, 215
Gargarisma, 25
Gas-gangrene antitoxins, 466
— — penicillin in, 503
— sulphonamides in, 333
Gastric secretory activity, histamine in, 365
Gastric ulcer, calcium carbonate in, 159
— — olive oil in, 44
Gastritis, hydrogen peroxide in, 130
— sodium bicarbonate in, 152
Gelatin, 47
Gelsemii radix, 269
Gelsemium, 269
Gentian, 53
— violet, 122
Germanin, 147, 489
Gestone, 448, 449
Gestyl, 439
Ginger, 69
Gitoxin, 336
Glacial acetic acid, 163
Glanduantin, 439
Glandubolin, 443
Glanducorpin, 448

Glanduitrin, 436
Glauber's salts, 83
Glaucoma, carbachol in, 288
— physostigmine in, 290
— pilocarpine in, 287
Glonoin oil, 294
Glucochloral, 209
Glucose, 49
Glucosides, definition of, 3
Glucosum liquidum, 49
Gluside, 51
Glycerin, 46
Glycerina, 13
Glycerinum acidi borici, 46 132
— — carbolici, 46
— — tannici, 46, 98
— amyli, 40, 46
— boracis, 46, 132
— croci, 137
— pepsini, 46, 75
— phenolis, 46, 113
Glycerophosphates, 419
Glycyrrhiza, 39
Goitre, iodine in, 174
Gold, 372
Gonadotraphon, 438
Gonadotrophic extracts, 438
Gonan, 439
Gonococcal infections,
nitrate of silver in, 371
sulphonamides in, 330
Gonorrhœa, penicillin in, 503
— potassium permanganate in, 131
Gossypium absorbens, 137
Goulard's extract, 367
— lotion, 367
— water, 367
Gout, cinchophen in, 357
— colchicum in, 356
Granulæ effervescentes, 25
Granuloma inguinale,
stibophenum in, 416
Graves' disease, 447
Gregory's powder, 86
Grey powder, 78, 389, 395
Ground-nut oil, 45
Growth hormone extracts, 439
Gum acacia, 39
— resins, definition of, 5
Gums, definition of, 5
Gunjah, 240
Guttæ, 25
Guy's pill, 340
Gynocardia oil, 135

Hæmolytic streptococci, sulphonamides in, 330
Hæmopoietin, 457
Hæmorrhage, opium in, 232
— neonatal, aceto menapthonum in, 489
— post-partum, oxytocin in, 438
Halibut-liver oil, 485
Halogen derivatives, 205, 206
Hamamelis, 100
Hartmann's solution, 164
Haschisch, 240
Haustus, 25
Hay fever, anti-histamine preparations in, 366
— — ephedrine in, 459
Heart failure, adrenaline in, 434
— — digitalis in, 340
— — mercury in, 397
— — opium or morphine in, 232
Heavy calcined magnesia, 80
— magnesium oxide 81
— metals, 366
Hemlock, 268
Henbane, 254
Heparin, 489
Hepatitis and sulphonamide therapy, 328
Heroin, 239
Herxheimer reaction, 411
Hexamine, 133
Hexobarbital, 219
Hexobarbitone, 219
Hexœstrol, 444
Histamine, 364
— phosphas acidus, 364
Histidine, 364
Hog's stomach, 455
Homatropine hydrobromide, 253
Honey, 51

Hookworm, betanaphthol in, 118
— calcium in, 161
— carbon tetrachloride in, 107
— tetrachlorethylene in, 109
— thymol in, 106
Hormone preparations, 419
Hydnocarpus oil, 136
Hydrargyri oxidum flavum, 390
— oxycyanidum, 390
— perchloridum, 390
— subchloridum, 391
Hydrargyrism, 398
Hydrargyrum, 389
— ammoniatum, 391
— oleatum, 391
Hydrates, 149
Hydrochloric acid, 162
Hydrocyanic acid, 351
Hydrogen citrate, 163
— peroxide, 129
Hydrophobia vaccine, 473
Hydrous ointment, 43
Hyoscine hydrobromide, 255
Hyoscyamine, 254
— sulphate, 255
Hyoscyamus, 254
Hyperpiesia, thiocyanates in, 354
Hypervitaminosis, 484
Hypnotics, 204
Hypoglycæmia, dextrose in, 50
Hypoglycæmic coma, pituitary extract in, 438
Hypophysin, 436

ICHTHAMMOL, 134
Ichthyol, 134
Icterus gravis neonatorum, vitamin K and, 487
Ileus, bile in treatment of, 102
— vasopressin in, 437
Impetigo contagiosa, gentian violet in, 122
— sulphonamides in, 334
Impotence, male, androgen therapy in, 451
Incompatibility of drugs, 30
Indian hemp, 240
— podophyllum, 95
Indicarminum, 140
Indigo carmine, 140
Infusa, 13
Injectio sodii citratis, anticoagulans, 488
— — — cum dextroso, 488
Injectiones, 13
Insecticides, 505
Insomnia, alcohol in, 189
— bromides in, 180
— chloral hydrate in, 208
— opium in, 234
Insufflationes, 25
Insulin, 451
— globin, 454
— protamine zinc, 454
Insulin coma, adrenaline in, 434
Insulinum, 451
Intestinal atony, prostigmine in, 290
Intocostrin, 273
Intracranial pressure, reduction of, hypertonic magnesium sulphate in, 82
Iodides, 173
Iodine, 126
— compounds of, thyroid, 424
Iodism, 174
Iodized oil, 175
Iodoform, 128
Iodophthalein, 176
Iodoxyl, 175
Ionization, 27
Ipecacuanha, 347
— præparata, 347
Ipomœa resina, 93
Iron, 382
— scale preparation, 383
Irradiated ergosterol, 482

JABORANDI leaves, 285
Jalap, 78, 93
Jalapa pulverata, 93
Jarisch-Herxheimer reaction, 411
Jasmine, yellow, 269
Jaundice, calcium chloride in, 160

Jaundice, Vitamin K in, 487
Jordan almond, 45
Juniper tar oil, 59

Kala-azar, antimony in, 415
Kaolin, 48, 380
Kaolinum, 380
Kemithal, 220
Keratosis, arsenical, 413
Kerosene, 505
Ketodestrin, 443
Ketohydroxyœstrin, 443
Kharsivan, 410
Kino, 99
Kola nut, 257
Kolpon, 443
Krameria, 99
Krescone, 439

Labour, induction of, castor oil in, 86
Lactic acid, 164
Lactoflavin, 480
Lactogenic hormone extracts, 439
Lactosum, 48
Lævulosum, 50
Lamellæ, 16
Lanolin, 40
— anhydrous, 40
Lard, 40
Lassar's paste, 375
Latin phrases, 508
Laudanum, 227
Laughing gas, 202
Lavender, oil of, 70
Laxative, sulphur as, 92
Lead, 367
— acetate, 367
— oxide, 367
— poisoning, 368
— — ammonium chloride in, 155, 171
— — calcium in, 160
Leishmaniasis, antimony in, 415
Lemon, 68
Leprosy, chaulmoogra oil in, 135
— hydnocarpus oil in, 136
Leptazolum, 62
Leukæmia, urethane in, 212
Levigation, 6
Lime, chlorinated, 124
— phosphate of, 157
— slaked, 157
— water, 157
Limonis cortex, 68
Linctus, 25
Linimenta, 16
Linimentum sinapis, 64
— terebinthinæ, 58
Linseed, 39
— oil, 39
Linum, 39
Lipiodol, 175
Lipo-lutin, 448
Liquores, 16
Liquorice, 39
Liver extract, 455
Lixiviation, 6
Loretin, 348
Lotio rubra, 376
Lotiones, 17
Lozenges, 23
Lugol's solution, 126
Luminal, 215
Lunar caustic, 370
Lupus erythematoses, gold salts in, 372
— — sulphonamides in, 333
Luteoantin, 439
Luteostab, 448
Lutocyclin, 448
Lycopodium, 48
Lymphogranuloma inguinale, sulphonamides in, 388
Lysol, 117

M. & B. 125, 318
M. & B. 693, 318
M. & B. 760, 319
Maceration, 6
Magnesia, fluid, 80
— heavy, 81
— light, 81
Magnesii carbonas, 80, 81
— oxidum, 81
— phosphas, 81
— sulphas, 80

Magnesii trisilicas, 81
Magnesium carbonate, 80, 81
— salts, 80
— tribasic phosphate, 81
— trisilicate, 81
Malaria, mepacrine in, 308
— methylene blue in, 140
— pamaquinum in, 307
— quinine in, 305
Male fern, 103
Malt, 50
— extract with cod-liver oil, 484
Mandelic acid, 168
Mandel's paint, 127
Manganese, 379
— butyrate, 379
Mania, hyoscine in, 256
— paraldehyde in, 210
Mantoux test, 471
Mapharsen, 411
Marc, 6
Marihuana, 241
Marris's test, 251
Mastitis, androgens in, 451
Maté, 257
Materia medica, definition of, 1
Meadow saffron, 354
Measures, 7
— metric, 8
Mecholyl, 288
Medicinal glucose, 49
— — zinc peroxide, 376
Medinal, 213
Mel depuratum, 51
Mella, 17
Menadione, 486
Menapthonum, 486
Menformon, 443
Meningitis, penicillin in, 503
— streptomycin in, 505
— sulphonamides in, 331
Meningococcal infections, sulphonamides in, 330
Menopause, œstrogenic therapy in, 446
Menorrhagia, androgens in, 451
Menstrual disorders, thyroid therapy in, 426
Menstruum, 6
Menthol, 63
Mepacrinæ hydrochloridum, 307
— methanosulphonas, 308
Mercurgan, 396
Mercurial cream, 390
— ointment, 390
— palsy, 398
— purgatives, 78
Mercurialism, 398
Mercurials, administration of, 397
Mercuric chloride, 390
— oleate, 391
— oxide, yellow, 390
— oxycyanide, 390
Mercurochrome, 396
Mercurous chloride, 391
Mercury, 389
— ammoniated, 391
— perchloride of, 390
Mersalylum, 394, 396
Metalloids, the, 402
Metals, heavy, 366
Methæmoglobinæmia, methylene blue in, 140
Methane hypnotics, 205
Methenamina, 133
Methyl alcohol, 190
— salicylate, 309
— strychnine, 264
— testosterone, 450
Methylated spirits, industrial, 190
Methylbrucine, 264
Methylene blue, 139
Methylis salicylas, 309
Methylphenobarbitonum, 216
Methylsulphonal, 211
Methylthebaine, 264
Methylthioninæ chloridum, 139
Methylthiouracilum, 428
Mexican scammony root, 92
Migraine, bellergal in, 364
— cholagogues in, 102
— ephedrine in, 459
— ergotamine in, 363
— œstrogenic therapy in, 446
Milk of sulphur, 91
— sugar, 48
Minderer's spirit, 154

Minimum lethal dose, 29
Misturæ, 18
Monkshood, 281
Morphinæ hydrochloridum, 227
— sulphas, 228
Moryl, 288
Mucilagines, 18
Mucilago acaciæ, 39
— tragacanthæ, 38
Muscarine, 287
Mushroom ; poisonous, 287
Mustard oil, 64
Myanesin, 275
Myasthenia gravis, ephedrine in, 459
— — physostigmine in, 290
Myocrisin, 372
Myoneural junction, 225
Myopathies, quinine in, 306
Myristica, 67
Myrrh, 66
Myxœdema, thyroid therapy in, 425

NAPHTHALENUM, 118
Naphthol, 118
Narceine, 237
Narcolepsy, amphetamine sulphate in, 460
— ephedrine in, 459
Narcotics, 181
— aliphatic, 204
— basal, 214, 218
Narcotine, 237
Nebulæ, 25
Nembutal, 218
Neoarsphenamina, 410
Neocinchopen, 357
Neohombreol, 450
Neokharsivan, 410
Neo-œstranol, 444
Neosalvarsan, 410
Neo-stibosan, 416
Neostigminæ bromidum, 289
— methylsulphatis, 289
Neptal, 397
Nephritis, pilocarpine in, 287
— sodium bicarbonate in, 152
— urea in, 147
Nephrosis, thyroid medication in, 426
Nervous system, action of drugs upon, 222
Neuralgia, alcohol injections for, 189
—inunction in 283, 285
Neuritis, peripheral, in sulphonamide therapy, 329
Neuro - muscular stimulants, 79
Neuropoietin, 457
Neurosyphilis, tryparsamide in, 409
Neutral principles, definition of, 3
Neutral proflavine sulphate, 121
Nicamide, 62
Nicotianin, 270
Nicotinamidum, 479
Nicotine, 270, 505
Nicotinic acid, 476
Night-blindness, vitamin A and, 476
Nikethamidum, 62
Nirvanol, 217
— sickness, 217
Nitrates, 155
Nitre, 155
— sweet spirit of, 293
Nitric acid, 162
Nitrites, 291
Nitritoid crisis, 411
Nitrogenii monoxidum, 202
Nitroglycerin, 294
Nitrous oxide, 202
Nobel's blasting oil, 294
Novarsenobillon, 410
Novasurol, 397
Novatophan, 357
Novocain, 280
Novurit, 397
Novutox, 281
Nucleic acid and nucleotides, 488
Nutmeg, 67
Nux vomica, 261
— — præparata, 261

OBESITY, mersalyl in, 397
— thyroid medication in, 426

Obstetrics, œstrogen therapy in, 447
— oxytocin in, 438
Octyl nitrite, 293
Oculenta, 18
Œstradiol, 443
— dipropionate, 443
— monobenzoate, 443
Œstrin, 443
Œstroform, 443
Œstrogens, 442
Œstronum, 443
Œstrosalve, 443
Oil, arachis, 45
— cajuput, 65
— cod-liver, 484
— cottonseed, 45
— halibut-liver, 485
— iodised, 175
— linseed, 39
— mustard, 64
— olive, 43
— rosemary, 66
— sesame, 45
Oil of almonds, 45
— of anise, 70
— of cade, 59
— of caraway, 71
— of chenopodium, 109
— of cinnamon, 68
— of clove, 67
— of coriander, 71
— of cubebs, 74
— of dill, 72
— of eucalyptus, 65
— of lavender, 70
— of lemon, 68
— of nutmeg, 67
— of peppermint, 70
— of phosphorus, 417
— of rosemary, 66
— of sassafrax, 66
— of theobroma, 138
— of turpentine, 58
Oils, fixed, definition of, 3
— volatile or essential, 4, 55
Ointments, 24
Olea, 18
Olefiant gas, 201
Oleic acid, 44
Oleo-resins, definition of, 5
Oleum amygdalæ, 45
— amygdalæ volatile purificatum, 45
— anethi, 72
— anisi, 70
— arachis, 45
— cadinum, 59
— cajuputi, 65
— cari, 71
— caryophylli, 67
— chaulmoogræ, 135
— chenopodii, 109
— cinnamomi, 68
— coriandri, 71
— crotonis, 95
— cubebæ, 74
— eucalypti, 65
— gossypii seminis, 45
— hydnocarpi, 136
— hydnocarpi æthylicum, 136
— hippoglossi, 485
— iodisatum, 175
— lavandulæ, 70
— limonis, 68
— lini, 39
— menthæ piperitæ, 70
— morrhuæ, 484
— myristicæ, 67
— olivæ, 43
— phosphoratum, 417
— ricini, 84
— rosmarini, 66
— sassafras, 66
— sesami, 45
— sinapis volatile, 64
— terebinthinæ, 58
— theobromatis, 138
Olive oil, 43
Omnopon, 237
Ophthalmia neonatorum, gonococcal, sulphonamides in, 330, 334
— — silver nitrate in, 371
Ophthalmology, silver proteinate in, 371
Opium, 226
— concentratum, 237
— pulveratum, 226
— toxicology of, 235
Orange peel, 54
Orasthin, 436

Orizaba jalap root, 92
Orthocaina, 280
Orthoform, 280
Osteomalacia, vitamin D, in, 485
Ouabain, 342
Ourari, 272
Ovarian extracts, 442
Ovendosyn, 444
Ovocyclin, 443
Ovostab, 443
Ox gall, 101
Oxycyanide, mercuric, 390
Oxygen, 171
Oxylan, 110
Oxymel, 51, 163
— scillæ, 342
Oxymella, 19
Oxytocin, 436, 438

PABESTROL, 444
Pain, relief of, opium and morphine in, 233
— — pethidine in, 238
Paludrin, 308
Pamaquinum, 307
Panama bark, 346
Pancreas, preparations of, 451
Pancreatin, 75
Pantopon, 237
Papaveretum, 237, 240
Papaverine hydrochloride, 237
Pa Ping, 161
Parachlormetaxylenol, 118
Parachlorometacresol, 117
Paraffin, hard, 41
— liquid, 41, 77
— ointment, 42
— white soft, 41
— yellow soft, 41
Paraform, 123
Paraldehyde, 210
Paralysis agitans, belladonna in, 251
— — amphetamine sulphate in, 460
— — hyoscine in, 256
— — stramonium in, 256
Parasiticide, sulphur as, 91
Parathormone, 429
Parathyroid extract, 429
Paregoric, 227
Parkinsonism. *See* Paralysis agitans.
Paroidin, 429
Paroleine, 41
Parrish's Food, 382
Pasta, 19
— zinci oxidi composita, 375
— — — cum acido salicylico, 375
Pastilli, 26
Pea-nut oil, 45
Pediculosis, 395, 507
Pellagra, vitamin B_2 and, 479
Pelletierine tannate, 104
Pemphigus, sulphonamides in, 333
Penicillin, 113, 497
Pentnucleotide, 488
Pentobarbital sodium, 218
Pentobarbitone, 218
Pentothal, 220
Pepper, 68
Peppermint, oil of, 70
Pepsin, 75
Peptic ulcer, aluminium hydroxide in, 382
— — atropine in, 250
— — magnesium trisilicate in, 250
Perandren, 450
Percaine, 281
Percentage solutions, 8
Perchloride of mercury, 390
Percolation, 6
Percoten, 434
Perles, 26
Pernocton, 218
Peru, balsam of, 73
Pessi, 26
Pethidinæ hydrochloridum, 238
Pharmaceutical processes, 6
Pharmacognosy, 1
Pharmacology, definition of, 1
Pharmacopœia, definition of, 2
Pharmacopœial preparations, 9
— — doses of, 27
Pharmacy, 1, 2
Pharyngitis, potassium chlorate in, 129

Phemitone, 216
Phenacetin, 296, 298
Phenazonum, 296, 298
Pheniodol, 177
Phenobarbital, 215
— soluble, 215
Phenobarbitonum, 215
— sodium, 215
Phenol, 113
— liquefactum, 113
Phenolphthalein, 78, 90
Phenol-rubrum, 141
Phenolsulphonphthalein, 141
Phenothiazine, 111
Phenyl-acetamide, 298
Phenyl-dimethyl-isopyrazolon, 298
Phenylglycollic acid, 168
Phenylhydrargyri nitras, 391
Phenylquinoline carboxylic acid, 356
Phenyl salicylate, 116
Phenytoinum sodium, 216
Phlebitis, dicoumarin in, 496
Phosphoric acid, 162
Phosphorus, 417
— poisoning, 418
— — copper sulphate in, 378
Phthalyl sulphathiazole, 335
Physiological saline solution, 145
Physolactin, 439
Physostab, 439
Physostigminæ salicylas, 289
Picrotoxin, 62, 266
Pigmenta, 26
Piles, galls and opium for, 99
Pilocarpine, 285
Pilulæ, 19
Pitocin, 436
Piton, 436
Pitoxylin, 436
Pitressin, 436
Pituitary extract, anterior lobe, 438
— — posterior lobe, 436
Pituitrin, 436
Pix carbonis præparata, 119
— liquida, 119
Plague vaccine, 472
Plasmochin, 307
Plasmoquine, 307
Plasters, 25
Plumbi acetas, 367
— monoxidum, 367
Plumbism, 367
Plumbum, 367
Pneumonia, oxygen in, 172
— pneumococcal, sulphonamides in, 331
Podophylli resina, 94
Podophyllum, 94
— indicum, 95
Poisonous compounds, 32
— mushroom, 287
Poisons Rules (1935), 35
Polyneuritis, vitamin B and, 476
Poppy petals, red, 137
Posology, 27
Potash, caustic, 148
Potassii acetas, 148
— bicarbonas, 148
— bromidum, 177
— chloras, 128
— chloridum, 146
— citras, 148
— et sodii tartras, 83
— hydroxidum, 148
— iodidum, 173
— nitras, 155
— permanganas, 130, 379
— tartras acidus, 84
Potassium, 148
— acetate, 148
— bicarbonate, 148
— bromide, 177
— chlorate, 128
— chloride, 146
— citrate, 148
— iodide, 173
— nitrate, 155
— permanganate, 130, 379
Powders, compound, 20
— dusting, 48
Pregnyl, 439
Prescribing, 30
Prescription, 32
Procainæ hydrochloridum, 280
Proctocaine, 280
Proflavinæ hemisulphas, 121
Progesterone, 448

Progestin, 448
Progestoral, 449
Progynon, 443
— B oleosum, 443
Prolactin, 439
Prolan, 439
Proluton, 448, 449
Prominal, 216
Prontosil album, 318
Prontylin, 318
Proseptasine, 318
Prostate, carcinoma of, œstrogens in, 447
Prostigmine, 290
Protamine insulinate, 454
Protargol, 370
Protein metabolism and salicylates, 311
Prothrombin and Vitamin K deficiency, 487
Prunus serotina, 353
Prussic acid, 351
Pseudo-ephedrine, 458
Psoriasis, chrysarobin in, 134
— dithranol in, 134
Pulveres, 19
Pulvis effervescens compositus, 83
— glycyrrhizæ compositus, 87
Purgatives, 76
— drastic, 92
Purpura, vitamin P and, 487
Pustulants, 55
Pyelectan, 175
Pyelitis, hexamine in, 133
— mandelic acid in, 168
— streptomycin in, 505
— sulphonamides in, 331
Pyloric stenosis, eumydrine in, 250
Pyramidon, 299
Pyrethrum, 505
Pyroxidine, 480
Pyroxylinum, 137

QUASSIA, 54
Quebrachine, 266
Quicksilver, 389
Quillaia bark, 346
Quinacrine hydrochloride, 307
Quinidinæ sulphas, 303
Quinidine, 301, 305
Quininæ et æthylis carbonas, 302
— bisulphas, 302
— dihydrochloridum, 302
— hydrochloridum, 302
— sulphas, 302
Quinine, 302
— and urea hydrochloride, 308
Quinophan, 356
Quinoxyl, 348

RADIUM, 400
Rat-bite fever, organic arsenicals in, 412
Raynaud's disease, carbachol and mecholyl in, 288
Rectified spirit, 184
Red poppy petals, 137
Refection in connection with vitamin B_1, 478
Relapsing fever, organic arsenicals in, 412
Renal efficiency, drugs used in tests of, 140, 147
Repercolation, 6
Resin, 60
— of scammony, 93
Resins, definition of, 5
Resorcinol, 123
Rhatany, 99
Rheum, 86
Rheumatic fever, salicylic acid in, 152, 313
— — sodium bicarbonate in, 152
— — sulphonamides in, 335
Rheumatoid arthritis, gold preparations in, 373
— — histamine in, 365
Rhinorrhœa, anti-histamine preparations in, 366
Rhœados petalum, 137
Rhubarb, 86
Riboflavin, 476, 480
Rickets, calcium lactate in, 160
— vitamin D and, 485
Rideal-Walker test, 111
Ringer-lactate solution, 164

Ringer's solution, 145
Ringworm, thallium in, 399
Rochelle salt, 83
Rosemary, oil of, 66
Roundworm, santonin in, 105
Roxenol, 118
Rubefacients, 55

SACCHARIN, 51
— soluble, 52
Saccharinum sodium, 52
Saccharum lactis, 48
— — purification, 48
Sacred bark, 88
Saffron, 137
Sal alembroth, 396
— ammoniac, 154
Salicin, 296, 309
Salicylic acid, 296
Salicylism, 312
Saline diuretics, 155
— purgatives, 79
— solution, normal, 145
— — physiological, 145
Salines, 77
Salol, 116
Salt action, 37, 143
— common, 145
Saltpetre, 155
Salvarsan, 410
Sal volatile, 154
Salyrgan, 396
Sanocrysin, 372
Santonin, 105
Sapo animalis, 139
— durus, 138
— mollis, 138
Saponins, 346
— definition of, 3
Sassafras oil, 66
Scabies, benzyl benzoate in, 316
— betanapthol in, 118
— sulphur ointment in, 92
Scaling, 6
Scammony, 92
— resin, 93
Scarlet fever antitoxic serum, 465
— — prophylactic, 466
Scarlet red, 118
Schick control, 463
— test toxin, 463
Schistosomiasis, stibophenum in, 416
Schultz-Charlton test, 465
Scilla, 342
Scleritis and sulphonamide therapy, 327
Scleroderma, mecholyl in, 288
Scopolamine hydrobromide, 255
Scott's ointment, 390
Scurvy, vitamin C and, 482
Seasickness, 251
Secale cornutum I.A., 357
Seidlitz powder, 83
Senega, 346
Sennæ folium, 87
Sennæ fructus, 87
Sensibamine, 360
Septicæmia, pencillin in, 502
— staphylococcal, sulphonamides in, 332
Sera, 460
Serogan, 439
Serum, antianthrax, 467
— antibotulinum, 467
— antimeasles, 466
— antiplague, 466
— antiscarlatinal, 465
— antivenosum, 466
Serum sickness, 460
Sesame oil, 45
Silver, 370
— arsphenamine, 410
— colloid, 371
— nitrate, 370
— proteinate, 370
Simple ointment, 43
Skin, action of volatile oils upon, 55
Skin diseases, arsenic in, 407
— — sulphur in, 92
— — thyroid in, 426
Small-pox lymph, 469
Snake bite, potassium permanganate in, 131
— venom antitoxin, 466

Soamin, 408
Soap, 138
— bark, 346
Soda, chlorinated, 124
— washing, 149
Soda lime, 158
Soda-mint tablets, 149
Sodii aminarsonas, 408
— aurothiomalas, 372
— benzoas, 314
— bicarbonas, 149
— bromidum, 177
— carbonas, 149
— — exsiccatus, 149
— chloridum, 145
— citras, 149
— et laurylis sulphas, 139
— et potassii tartras, 83
— hydroxidum, 149
— iodidum, 173
— metabisulphis, 136
— morrhuas, 485
— nitris, 295
— phosphas, 83
— — acidas, 163
— salicylas, 309
— sulphas, 83
— — exsiccatus, 83
Sodium, 149
— aminarsonate, 408
— amytal, 217
— aurothiosulphate, 372
— barbitone, 213
— benzoate, 314
— bicarbonate, 149
— bismuthyl tartrate, 403
— borate, 132
— bromide, 177
— carbonate, 149
— chloride, 145
— citrate, 149
— dehydrocholate, 102
— dihydrogen phosphate, 163
— hydroxide, 149
— indigotindisulphonate, 140
— iodide, 173
— lauryl sulphate, 139
— metabisulphite, 136
— morrhuate, 485
— nitrite, 295
— nucleinate, 488
Sodium, phosphate, 83
— potassium tartrate, 83
— salicylate, 309
— salts, 83
— sulphate, 83
Solestrin, 443
Soluble fluorescein, 140
— phenytoin, 216
Soluseptasine, 317, 318
Solutions, percentage, 8
Soneryl, 214
Soporifics, 181
Sore throat, iron in, 386
Spirit, rectified, 184
Spiritus, 20
— ætheris, 198
— — nitrosi, 293
— methylatus industrialis, 190
Spray paraffin, 41
Sprue, liver or stomach therapy in, 457
Squill, 342
Standardizing, 7
Staphylococcus toxoid, 466
Starch, 40
Sterility, progesterone in, 449
— vitamin E and, 486
Stibophenum, 416
Stibosan, 416
Stilbœstrol, 444
— dipropionate, 444
Stomach, desiccated, 455
Stomatitis, kaolin in, 381
— potassium chlorate in, 129
Storax, 74
Stovarsol, 408
Stramonium, 253
Streptocide, 318
Streptococci, hæmolytic, sulphonamides in, 330
Streptomycin, 504
Strophanthin—G, 342
Strophanthinum, 341
Strophanthus, 341
Strychni semen, 261
Strychnine, 261
— hydrochloride, 262
— poisoning, 265
— — bromides in, 180
— — charcoal in, 170
Styrax, præparatus, 74

Succinyl sulphathiazole, 320
Sucrosum, 48
Sugar, 48
— of lead, 367
Sulfosin, 92
Sulphacetamidum, 318
— sodium, 318
Sulphadiazina, 319
Sulphaguanidina, 319
Sulphamerazine, 320
Sulphamezathine (sulphadimethylpyrimidine), 319
Sulphanilamide, 316, 318
Sulphapyridine, 318
Sulpharsenobenzene, 410
Sulpharsphenamina, 410
Sulphathiazolum, 319
Sulphocyanates, 354
Sulphonal, 211
Sulphonamides, 113, 316, 320
— absorption, distribution, excretion and metabolism of, 322
— activity, 321
— administration, 324
— dosage, 329
— reactions to, 326
— therapy, general principles of, 324
Sulphones, 205, 211
Sulphur, 78, 90
— præcipitatum, 91
— sublimatum, 90
Sulphuric acid, 162
Sulphurous acid, 124
Sunstroke, 144
Suppositoria, 21
Supracort, 434
Suraminum, 147, 489,
Surgery, sulphonamides in, 334
Suspension, definition of, 6
Sweet almond, 45
Sweet spirit of nitre, 293
Sycosis barbæ, pencillin in, 501
Symbols, 7
Sympathin, 223, 224
Synapoidin, 439
Syntestrin, 444
Synthovo, 444
Syphilis, bismuth in, 405
Syphilis, iodides in, 174
— mercury in, 396
— organic arsenicals in, 411
— penicillin in, 504
Syrup of wild cherry, 354
Syrupi, 21
Syrupus 48,
— glucosi liquidi, 48

T.A.B. vaccine, 472
Tabacum, 270
Tabellæ, 21
Tachycardia, paroxysmal, carbachol in, 288
Taka-diastase, 76
Talc, 48
Tannic acid, 98
Tapeworm, anthelmintics for, 103
Tar, 119
Tar camphor, 118
Tartar emetic, 413
Tartarated antimony, 413
Tartaric acid, 164
Tea, 257
Teeth, faulty development of, vitamin A deficiency and, 476
Terebenum, 73
Terpineol, 73
Terpini hydras, 73
Testicular extracts, 450
Testis, undescended, gonadotrophin in, 441
Testosterone, 450
— propionate, 450
Testoviron, 450
Tetanus, antitoxin, 463
— bromides in, 180
— magnesium sulphate in, 82
— paraldehyde in, 211
— pentobarbitone in, 219
— prophylactic, 465
— sulphonamides and, 335
— toxoid, 465
Tetany, calcium chloride in, 160
— parathyroid extract in, 430
Tetracaine, hydrochloride, 281
Tetrachlorethylene, 109

Tetrachlormethane, 107
Tetraiodophenolphthalein, 176
Tetronal, 212
Thalii acetas, 399
Thallium, 399
— acetate, 399
Thebaine, 239
Theelin, 443
Theobroma, oil of, 138
Theobromina et sodii salicylas, 260
Theocine, 260
Theophyllina, 260
— cum æthylenediamina, 260
— et sodii acetas, 260
Therapeutic ratio, 29
Therapeutics, definition of, 1
Thiamine hydrochloride, 475
Thiazamide, 319
Thiocyanates, 354
Thiopentone, 220
Thiouracil, 428
— methyl, 428
— propyl, 428
Thorium, 401
Thorotrast, 401
Threadworm, 110, 122, 140
Thrombocytopenia in sulphonamide therapy, 329
Thrombo-phlebitis migrans, dicoumarin in, 496
— heparin in, 492
Thrombosis, dicoumarin in, 495
— heparin in, 491
Thrush, glycerinum boracis in, 133
— sodium metabisulphite in, 136
Thujon, 56
Thymol, 106
Thyrogan, 439
Thyroid gland, 424
Thyroideum, 424, 425
Thyrotoxicosis, iodine in, 127
— thiouracil in, 428
Thyrotrophic hormone extracts, 439
Thyrotropin, 439
Thyroxine, 424
Thyroxinum, 424
Tinctura antiperiodica, 307
Tincturæ, 23
Tobacco, 270
Tolerance, drug, 28
Tolu, balsam of, 73
Tonephrin, 436
Tonitrin, 436
Totaquina, 301
Toughened caustic, 370
Toxicology, definition of, 1
Toxins, 460
Toxinum diphthericum calefactum, 463
— — detoxicatum, 462
— — diagnosticum, 463
— — staphylococcicum detoxicatum, 466
— tetanicum detoxicatum, 465
Toxoid-antitoxin, 462
Tragacanth, 38
Tribromoethyl alcohol, 190
Trichloracetic acid, 163
Trichloroethylene, 202
Trichloromethane, 192
Trilene, 202
Trimethylamine, 357
Trinitrin, 294
Trinitroglycerin, 294
Trional, 211
Triple dye for burns, 122
Trochisci, 23
Trypanosomiasis, antimony in, 415
— suramin in, 147
— tryparsamide in, 409
Tryparsamide, 408
Tuberculin,
— old (T.O.), 469, 470
— P.P.D., 469
— Rückstand (T.R.), 470
Tuberculinum pristinum, 469
Tuberculosis, gold salts in, 372
— streptomycin in, 505
Tubocurarine, 273
Tularæmia, 505
Turpentine, oil of, 58
Tympanites, carbachol in, 288
Typhoid fever, cold baths in, 143
Typhus, D.D.T. in, 507

Typhus, vaccine, 472
Tyramine, 357

UNDEN, 443
Unguenta, 24
Unna's paste, 375
Uradal, 221
Uræmia, calcium in, 160
— pilocarpine in, 287
Urari, 272
Urea, 147
— derivatives, 205, 212
Urethane, 212
Urinary antiseptics, 74, 111, 133, 311
— infections, penicillin in, 503
Urine, retention of, carbachol in, 288
— suppression of, sodium sulphate in, 84
Uropac, 175
Uroselectan B, 175
Urotropine, 133
Urticaria, anti-histamine preparations in, 366
— calcium in, 161
Uteritrin, 436
Uterus, vegetable drugs acting upon, 357

VACCINAL encephalitis, 469
Vaccine, B.C.G., 471
— cholera, 472
— hydrophobia, 473
— lymph, 469
— plague, 472
— T.A.B., 472
Vaccines, 467
— autogenous, 468
— defatted, 468
— detoxicated, 468
— diaplyte, 468
— sensitized, 467
— stock, 468
— tubercular, 469
Vaccinum febris flavæ, 471
— pestis, 472
— typho-paratyphosum, 472
— vacciniæ, 469
Vaginitis, acetarsol in, 409
Valerian, 72
Vapores, 26
Varicose ulceration, mecholyl in, 288
— — Unna's paste in, 377
Varicose veins, æthanolamine in, 44
— — dextrose in, 50
— — quinine and urethane in, 306
— — sodium morrhuate in, 485
— — sodium salicylate in, 313
Vasopressin, 436
Veganin, 239
Ventriculin, 455
Ventriculus desiccatus, 455
Veratrine, 284
Veronal, 212
Vesicants, 55
Vienna paste, 159
Vina, 26
Vincent's angina, organic arsenicals in, 412
— — penicillin in, 501
Vinegar of squill, 342
Vinesthene, 201
Vinyl ether, 201
Vioform, 348
Viola crystallina, 122
Virginian prune bark, 353
Viride nitens, 122
Virormone, 450
Vitamin A, 475, 482
— B, 476
— C, 481
— — indicator, 141
— D, 482
— E, 486
— K, 486
— P, 487
Vitamin, antineuritic, 477
— antirachitic, 485
— antiscorbutic, 482
— antisterility, 486
— growth promoting, 475
— pellagra preventive, 479
— preparations, assay, 474
Vitamins, 474
Vitriol, elixir of, 162

Volatile oils, 55, 58, 67, 72, 73, 74
— — definition of, 4
Von Heyden 471...416
— — 693b...416
— Pirquet test, 471
Vulvo-vaginitis, sulphathiazole in, 331

Warburg's tincture, 307
Washing soda, 149
Water, distilled, 142
— for injection, 142
Wax, 42
Waxes, definition of, 4
Weights and measures, 7
— metric, 8
White precipitate, 391
— — ointment, 391
Witch-hazel, 100
Wood charcoal, 169
— spirit, 190
— tar, 119
Wool-fat, 40, 43, 100
Woorali, 272
Woorara, 272
Wound sepsis, sulphonamides in, 334
Wounds, penicillin in, 501, 503

Xerophthalmia, vitamin A deficiency and, 475

Yatren, 348
Yaws, organic arsenicals in, 412
— tartar emetic in, 416
Yellow fever vaccine, 471
Yellow jasmine, 269
Yellow mercuric oxide, 390
Yohimbine, 266

Zinc, 375
— oleate ointment, 375
Zinci chloridum, 375
— oxidum, 375
— peroxidum, 376
— stearas, 375
— sulphas, 375
Zinc-protamine-insulin, 454
Zingiber, 69

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